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THE USE OF HEPARIN AS AN ANTI-INFLAMMATORY AGENT.*†‡

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INTRODUCTION.

Numerous experiments in our laboratories which have been published in detail elsewhere[1,2] indicate that heparin has a marked capacity to bind endogenously released histamine. In addition, its capacity to bind certain other basic substances (histamine releasers) has been well established by both *in vitro* and *in vivo* experimentation.[3] Other studies indicate that heparin has a dramatic life-preserving effect in animals given lethal doses of histamine releasers, such as Polymyxin, 48/80, snake venoms, etc.[2] It has been stated that histamine is free or protein bound in cells and that sulfated ground substance binds extracellular histamine. The extracellular histamine can be released and when free, exerts its biological effects. Heparin acts in the nature of a biological exchange mechanism in which its release from extra or intracellular

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sites, results in a greater availability of binding sites for histamine.[4] This binding of the histamine prevents its setting off a generalized stress response.[1,4] Similarly, serotonin, which is probably the natural edema and inflammation producing agent in the rat and mouse[5] is also bound by sulfated mucopolysaccharides. Its participation in the human is, of course, well established.[6] Heparin thus has a more, or at least as fundamental a property as a biological ion exchanger as its role in anticoagulation.

It seemed important to ascertain whether heparin had any therapeutic effect in the human, particularly in those conditions in which histamine release and the allergic inflammation which results from it, may be the primary cause of the malady. Thus, several types of allergic and inflammatory diseases were treated with heparin or heparin combined with either polymyxin, neomycin or streptomycin. It had previously been shown that combinations of heparin and these antibiotics did not eliminate the antibiotic capacities of the drugs bound to heparin.[7] Lesions that could be observed directly, such as those on the skin, or systemic effects as in asthma and hay fever, were studied to ascertain whether these clinically observed types of allergic inflammations could be blocked by the administration of heparin. The cases described here were treated according to the methods outlined below.

MATERIALS AND METHODS.

Since, of all the allergic states, weeping eczema of the ear could be most easily examined, it was chosen as the first allergic disease to be treated by heparin. Clinically, aural weeping eczema may be divided into two types: one type will respond to almost any medication and will clear quickly; a second type is very resistant to all treatments. Only cases treated unsuccessfully by competent otolaryngologists and/or dermatologists for a period of at least two years were selected for trial by the heparin.

Cultures of the existing organisms were taken before the treatment was started. Commonly found organisms were hemolytic staphylococcus, proteus vulgaris or pseudomonas

aeruginosa. After the identification of the organisms, their sensitivities to the appropriate antibiotic were determined. When possible, the alkaline antibiotics of choice and hydrocortisone were used for the treatment. Prior to this, all the usual treatments such as hot packs, argyrol, etc., had been tried unsuccessfully; therefore, no attempt was made to repeat their use. If the hydrocortisone and antibiotic treatment was successful, the subject was not accepted for trial on heparin.

Hemolytic staphylococci were inoculated on blood agar plates.[8] The blood agar was prepared in three ways: in one, discs of neomycin, polymyxin and streptomycin were placed on a standard blood agar plate, inoculated with the hemolytic staphylococcus aureus. The area of clearing about the discs was measured. In a second plate, the discs were first saturated with heparin and then placed on the agar, and finally, on the third plate discs were placed on the blood agar to which heparin had been added. The clearing in the last two was slightly greater than on the first plate. Heparin either has antibiotic effects of its own or possibly it permitted the diffusion of the antibiotic across the blood agar more easily and, therefore, dissemination was increased and the area of clearing enlarged. Possibly both mechanisms may occur. Further investigation of the antibiotic role of heparin is being pursued. Heparin did not inhibit the action of any of the antibiotics tested.

In order to treat the patients selected, a 3 per cent mixture of the appropriate antibiotic was suspended in 2½ per cent hydrocortisone solution, and 1 per cent heparin.* In the later work, Bro-Parin† and a mixture supplied by the Darwin Laboratories‡ were used. Bro-Parin contains neomycin, polymyxin and heparin. The mixture prepared by Darwin Laboratories for our use contains dihydrostreptomycin 2 per cent; hydrocortisone .25 per cent; neomycin 2 per cent, and heparin 1 per cent. Dihydrostreptomycin was substituted for polymyxin in this preparation because other studies to be published

*Supplied by Mr. Gil Ayron of Broemmel Pharmaceuticals.
†Trade name for the mixture given here. Broemmel Pharmaceuticals.
‡Supplied by Mr. Leon Freeman, Darwin Laboratories.

indicate that dihydrostreptomycin had a wider range of antibiotic activity.

RESULTS.

Table I shows that 31 cases of infectious external otitis were treated. These were divided into two categories: the first category had 12 cases which showed infection only; a second category of 13 patients contains those with infection and weeping eczema. Bacteriological studies showed organ-

TABLE I.

External Otitis Media.

No. Cases	Sex M	Sex F	Infection Alone	Infection + Allergy
31	15	16	12	"
			Neomycin Sensitivity	Neomycin Sensitivity
			6	12
			Streptomycin Sensitivity	Streptomycin Sensitivity
			6	7

Results:

Infection Alone						Infection and Allergy					
Neomycin Sensitivity			Streptomycin Sensitivity			Neomycin			Streptomycin		
1	2	3	1	2	3	1	2	3	1	2	3
0	4	2	0	1	5	2	2	8	0	1	6

isms sensitive to either neomycin or streptomycin, as well as the other antibiotics. These antibiotics were chosen because their alkaline structure allowed a complex with heparin.

Results of the treatment are given in three categories: *1.* Shows very poor results. *2.* Indicates moderately successful treatment. *3.* Excellent curative findings. There were only two unsuccessful cases, both treated with the neomycin preparation. It was interesting to note that two other patients had only fair results with the neomycin ointment, but following substitution of the streptomycin complex had complete clearing of infection.

After being convinced that weeping allergic lesions re-

sponded satisfactorily to the heparin antibiotic complexes, it was determined to ascertain whether other allergic states more difficult to observe would similarly show curative effects. Heparin,* therefore, was tried in cases of acute pollinosis. Amounts varying from 100 mg. to 300 mg., depending upon the size of the patient, were injected intravenously into eight patients during acute attacks of hay fever (see Table II).

Table II illustrates ten cases of patients with pollinosis selected for treatment. Four of them in addition to the pol-

TABLE II.

Hay Fever.

No. Cases	Sex M	Sex F	Polinosis	Polinosis and Sinusitis	Polinosis + Catarrhalotitis Media
10	4	6	5	4 (1 w/polyps)	1

Results:

Nasal Discharge			Nasal Obstruction			Headache			Conjunctivitis			Breathing Eased			Redness and Itching		
1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3
0	4	3	0	1	8	0	2	2	0	1	5	0	2	4	0	0	7

1. Results graded: 1—poor; 2—medium; 3—excellent responses.

2. Sinusitis had failed on antibiotic and steroid. With 100/mg. heparin added every other day, sinuses were clear in a week; no discharge after four weeks. Polps shrank in one case. Catarrhal otitis media cleared with 200 mg. heparin i.v. for four days, then no longer response of ear.

3. Treated with 150-300 mgs. heparin i.v. and given appropriate antibiotic and steroid. Two patients received 150 mgs. i.v.; one patient 175 mgs. i.v.; five patients were given 200 mgs. i.v.; one, 300 mgs. i.v. and one patient was given 100 mgs. i.m. every day for four weeks.

linosis, had sinusitis—one with polyp formation. The last patient had a catarrhal otitis media. Symptoms of nasal discharge, nasal obstruction and headache were relieved within ten minutes after administration of the heparin. In the patient with polyps, after acute symptoms had subsided, cultures were taken of the exudate from the sinuses. The appropriate antibiotic was selected and given in combination with prednisolone. This treatment was ineffective. When heparin (100 mgs. i.m./day) was added and the antibiotic and steroid were continued, the polyps began to shrink, and at the end of a four-week period had substantially disappeared. The infection

*Supplied by Dr. Samuel Anderson, Abbott Laboratories and Mr. Leon Freeman of Darwin Laboratories.

subsided, so that no further pus could be obtained even after shrinking the nose.

The patient with catarrhal otitis media was treated with 200 mg. of heparin intravenously on four separate occasions. In each case the ear would clear, only to refill slowly at first; after several treatments it filled more rapidly. After the fifth treatment heparin was no longer successful in eliminating the fluid. It was felt that higher doses of heparin might result in too great an anti-coagulant effect and leaving fluid in the ear might result in permanent impairment of hearing. The older treatment of mechanical removal was employed alone as it was deemed possible that heparin treatment could increase bleeding at the site of incision.

In three of the cases, placebos were given at various times instead of the heparin. In no case did the patient's symptoms respond to the placebo, but when followed by heparin at periods of about 15 minutes, relief of symptoms occurred promptly. One patient who had a sensitivity to beef protein, developed hives after using the heparin on two occasions. She had had relief of her hay fever with the heparin, but we were unable to continue its use because of the allergy, either to the heparin or to the tissue from which it was extracted.

Finally, 12 patients with acute recurrent asthmatic attacks were selected for trial. In one, 100 mg. was given subcutaneously. In the remainder, 150 to 300 mg. was given intravenously, depending upon the size of the patient. There was marked, almost immediate relief of the respiratory distress (see Table III).

Table III is an analysis of the attempts to relieve the attacks of acute asthma. Ten patients were included in this group. The dosage again varied from 150 to 300 mg. of heparin given intravenously at the time of an acute attack of asthma. In nine of the patients there was immediate relief from wheezing, cough, and on difficulty in breathing. There was a decrease in the panic which affected six patients. It is interesting to note that eight of the patients commented spontaneously of a feeling of warmth in their chests. The

hay fever victims, when given the heparin, commented on the sense of warmth in their heads.

In one patient there was a failure of heparin to secure a remission of the acute attack. The asthma in this patient is believed to be on a neuropsychiatric basis, as detailed hospital studies revealed no true lung pathology. After heparin had been given, wheezing could not be induced by the cough, which usually precipitated an attack. If, however, he once precipitated the attack and started coughing and wheezing, the heparin had no effect on his asthma. It was felt that the at-

TABLE III.

Acute Asthma.

No. Cases	Sex		Treatment mgs. Heparin i.v.			
	M	F	150	200	250	300
10	4	6	1	4	3	2

Results:

Wheezing			Cough			Breathing Eased			Panic Decrease*			Feeling Warmth†		
1	2	3	1	2	3	1	2	3	1	2	3	1	2	3
1	3	6	1	5	4	1	3	6	1	4	2		2	6

*Three patients did not comment.
†One patient did not comment.

tacks were initiated by mental stimulation, since asking him questions on problems he did not choose to answer were avoided by coughing and wheezing.

The action of the heparin is felt to be almost immediate. As in the cases of experimental animals, heparin counteracted the histamine released in patients having acute asthmatic attacks. Other drugs which were inadequate alone were then able to maintain an asymptomatic patient. This was especially true of a mixture of antibiotics and steroids in infections, and of the steroids alone in the allergic conditions.

One of the authors, being asthmatic, injected himself with 200 mg. of heparin intravenously during an acute attack. Almost immediately there was a sensation of warmth starting at the site of injection and spreading through the body, but centering chiefly in the chest. There was a tremendous feel-

ing of relaxation and in several moments the breathing eased off. The sense of panic, which asthma seems always to induce, disappeared and was followed by a markedly relaxed state with normal breathing. The sense of warm relaxation without wheezing was the outstanding feeling left by the heparin.

Quantitative evidence for the action of heparin on relief of acute asthma has been obtained by Dr. Jerome Cohn.[15] Preliminary investigation has shown that heparin almost immediately decreases bronchiolar resistance to air flow in acute asthma resulting in increased vital capacity in six patients. These investigations are being continued and will be reported in detail later.

DISCUSSION.

Essentially, the difference between local inflammation and stress is quantitative. Within a volume of local inflamed tissue cellular destruction is limited to the area, whereas in stress there is a generalized cell destruction with a great release of the same cytotoxins. Injury to one type of cell may affect the function of neighboring cells through the inflammatory response. As cells are destroyed, they in turn, release cytotoxins which bring about the destruction of the adjacent cells, so that a chain reaction of cellular destruction occurs.[9]

These altered states of the tissues, despite their protective effects, can be termed "intoxication," since it is inimical to the continuance of normal function of the tissue. It is well recognized that histamine and serotonin are markedly inflaming substances. They are contained both intra-cellularly and extracellularly.[10] A hypothesis has been proposed elsewhere[10] that histamine or other amines having similar cytotoxic effects, are released from the cell upon injury. They, therefore, accumulate in increased amounts in extracellular tissue. As this increase takes place, more toxic amines are available to attack adjacent cells, and a chain reaction of cellular destruction occurs.

Whatever the theoretical possibilities may be, it is known that histamine is released in various allergic states, including local and generalized anaphylaxis. Thus, endogenous release

of histamine occurs following chemical or bacterial poisoning, thermal and traumatic wounds, and may be released from cells upon antigen antibody union. Despite the arguments and conflicting data concerning the participation of histamine in physiological states, there seems to be relatively little debate that histamine, serotonin and other amines participate and actually initiate inflammation, particularly the inflammation induced in allergy.

If the chain reaction of cell destruction was permitted to continue undisturbed, the organism would always die. There are three main mechanisms known at present which prevent the lethal accumulation of cytotoxin. The first is excretion of histamine from its site of release and from the body.[11] The second is the action of the steroids and the third, local detoxification. Since the stimulus for histamine release is almost always endogenous, the tissues must be frequently exposed to toxic amines. A local mechanism must exist to buffer or destroy the toxic amines interstitially. The earliest changes seen in loose connective tissue response to the toxic amines is the destruction of mast cells. This is followed by the granules being picked up by the fibroblasts and digested.[1] Heparin as well as histamine, is found in these granules.[5] The capacity of heparin to complex with histamine and thus inhibit the cytotoxic effect of this substance may be a detoxifying mechanism.

It may be seen, then, that any means by which the histamine concentration of the tissue would be reduced would thereby reduce the inflammatory potential, providing the stimulus for the production of the inflammation were held constant. The less the histamine available for release in the tissue, the less the degree of inflammation. Heparin, in this way, acts as an anti-inflammatory substance. It appears that the anti-inflammatory effect of heparin is not so much concerned with the immediate catabolism of histamine, but rather with the capacity of heparin to complex with this base. Not only does heparin complex histamine, but probably other amines such as serotonin.[12]

It may be that heparin is somehow related to the eventual

disposition or catabolism of histamine, but this does not account for its immediate detoxifying effect. The anti-inflammatory role of heparin is thus in marked contrast to that of the steroids, in that adrenal cortical steroids apparently do not inhibit the release of histamine upon the initiating stimulus[13] or bring about its eventual catabolism. They probably stop the continuous addition of histamine to the extracellular pool by preventing the toxic effect of histamine on the cell and thereby they inhibit the chain reaction of histamine release from destroyed cells. In this respect, it is interesting to note that in some allergic states heparin actually possesses a more marked anti-inflammatory effect on certain allergic induced inflammations than that possessed by the adrenal cortical steroids.

Heparin provides protection against endogenous histamine released by basic substances such as polymyxin B or other alkaline antibiotics, 48/80, and snake venom. If these substances are administered to mice in lethal doses, it has been found that the lethality can be prevented either before or after injection of the histamine releaser by administration of heparin.[14] A movie has been made in our laboratory which illustrates these actions of heparin.[14] Heparin acts in respect to inhibiting the lethal consequences of endogenously released histamine in a linear dose response fashion[2]; thus, there is a stoichiometric relationship existing between the concentration of the histamine releaser and the protective agent heparin.

Studies performed in our laboratories indicate that the protective role of heparin is primarily due to the sulphuric acid substitution of this polymer.[15] Other sulphated carbohydrate polymers such as chondroitin sulphate, agar agar and various synthetic suphated polysaccharides, will also provide protective effect against histamine release.[15] It is thus apparent that heparin and other sulphated polysaccharides act as biological ion exchangers and essentially follow the law of mass action.

It is of significance that although there may be a relation between the anti-inflammatory effects of the steroid hormones

and heparin, it is very apparent that the mechanisms of anti-inflammatory action are entirely different.

CONCLUSIONS.

1. Laboratory work showed that heparin and other sulphuric acid substituted polysaccharides possess the ability to neutralize histamine by acting as ion exchangers following the law of mass action, by the formation of a heparin histamine complex. *2.* Studies of the effect of heparin added to previously unsuccessfully tried steroids and antibiotics helped clear infected external otitis, with and without weeping eczema. *3.* Selected cases of acute hay fever and asthma were helped by the intravenous administration of heparin. As the acute attack subsided, more permanent relief was established by the classical methods of treatment. *4.* There was sufficient clinical improvement to warrant further studies to check on the hypothesis that sulfated polysaccharides, especially heparin, can provide protection against endogenous histamine release, suggesting a basic protection at least as important as that of anti-coagulation. *5.* Combinations of alkaline antibiotics and heparin are valuable agents since the complex possesses the antibiotic activity and as antibiotic is released from the complex, heparin, in turn, is available to complex histamine and thereby prevents the noxious effects of this substance.

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GILL MEMORIAL EYE, EAR AND THROAT HOSPITAL.

The Gill Memorial Eye, Ear and Throat Hospital has just completed its Thirty-Third Annual Spring Congress in Ophthalmology and Otolaryngology and allied specialties. The attendance was one of the largest in the history of the school with an attendance of 300 doctors and their wives. There were 40 states, including Canada, represented. There was a total of 18 guest speakers and there were 50 lectures during the five-and-a-half days of the Spring Congress. In 1961, the Thirty-Fourth Annual Spring Congress will be held from April 9 through April 14.

VASODILATOR THERAPY IN SENSORY-NEURAL HEARING LOSS.*†‡

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Individuals developing an obscure sudden unilateral or bilateral sensory-neural (perceptive) hearing loss have been the object of much medical treatment for a number of years. This treatment has been based on the assumption that the loss of hearing was due to a vascular accident in the inner ear. Very little information has appeared in the literature as to the results of this treatment. One purpose of this paper is to present the findings in a group of patients with sudden hearing loss of the sensory-neural type and to show their response to an intensive vasodilator regime.

Some otologists[1,2,3a,3b] have stated that treatment is usually ineffective in this group of patients. Others[3c] feel that treatment, to be effective, *must* be initiated within a few hours of the onset of the hearing loss. A second purpose of this paper is to point out that treatment *does* seem to be effective in a significant percentage of these individuals. Although early treatment is undoubtedly more effective, treatment instituted after five or six weeks may still result in the return of serviceable hearing.

MECHANISM OF HEARING LOSS.

Many theories have been advanced as to the cause of sudden neural or end organ deafness of obscure origin. Some otologists[4,5,6] have felt that the etiology was a viral infection or a neuritis. The majority,[3c,7,8,9,10,11] however, believe that sudden loss is due to a disturbance of the vascular bed in the

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†From the Otologic Medical Group and the Department of Otolaryngology, University of Southern California School of Medicine.

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inner ear. Such disturbances include sludging of blood, hemorrhage, thrombosis, arteritis, embolism, spasm, edema, and combinations of these. If due to hemorrhage or thrombosis, then very little can be expected in the way of recovery. If due to spasm and edema, however, early treatment should be effective. Unfortunately, a differential diagnosis between these two types cannot be made at present. Treatment is, therefore, advocated on the assumption that the sudden loss is due to vascular spasm.

The mechanism of spasm appears to be autonomic dysfunction as described by Williams[10,12] and Hilger.[11] There is a localized area of arteriolar spasm associated with dilatation of the capillaries and venules. Anoxia of the capillary loop then develops. This anoxia results in injury to the endothelium, sludging of blood, release of toxic substances and increased permeability of the capillary loop. A local disturbance of the electrolyte and fluid balance develops, resulting in endolymphatic (and perilymphatic?) hydrops or hypertension. The autonomic nerve supply of the end-organ is not clearly understood, but clinical experience indicates that in most cases the spasm seems to be of cholinergic origin.[13]

THERAPY.

Treatment is based on the assumption that autonomic dysfunction and the resultant vascular bed disturbance is the cause of the hearing loss and is reversible. There are three factors that must be considered in each case: the underlying or precipitating factor, the neurovascular dysfunction, and the edema.

Underlying or Precipitating Factors: Stress, fatigue, emotional disturbances, allergy, endocrine imbalance—one or all of these have been considered to be of importance as underlying or as precipitating factors.[8,9,10,11] Recently Shambaugh[14] reported a number of cases that had been unresponsive to vasodilator therapy, but that responded well to thyroid medication. In the author's experience there has often been an episode of severe fatigue or emotional disturbance just prior to the onset of a sudden hearing loss. If the sudden loss is of

a fluctuating character, this fluctuation can frequently be related to repeated emotional episodes.

Neurovascular Dysfunction: In sudden hearing loss, specific drug therapy is directed primarily towards the neurovascular problem. Hilger,[11] in an excellent paper on inner ear therapy, divided drugs affecting the neurovascular tone into two groups: the autonomic blocking agents and the smooth muscle dilators. The autonomic blocking agents that have been used are banthine, procaine, atropine, priscoline and ergots. Smooth muscle dilators include nicotinic acid, histamine, nitrites and papaverine. Various combinations of these drugs have been used by most otologists. Some[15,16] have induced stellate ganglion block with procaine and, if favorable response is obtained, have recommended upper dorsal sympathectomy as definitive treatment.

Edema: To relieve the edema due to vasospasm, a low salt diet, at times with a diuretic, has been recommended. Immediate fenestration of the horizontal semicircular canal to decompress the labyrinth has been advocated by some.[17]

VASODILATOR REGIME.

A standard vasodilator therapy has been used in all of the 247 patients with a sensory-neural hearing loss in this series. The regime is also used in cases of Ménière's disease and recurrent spontaneous or postural vertigo.

Histamine: Intravenous histamine is given on three consecutive days. This solution* contains 2.75 mgs. of histamine phosphate in 250 cc. of normal saline. The solution is administered at an initial rate of 20 to 30 drops per minute, and if well tolerated, this may be increased to 50 to 60 drops per minute after five minutes. The time of administration is 90 minutes in the average case. The patient is made aware that a mild flushing, headache, and increased head noise may develop. Following completion of this i.v. series, 0.1 cc. of 1:100,000 dilution of histamine phosphate is administered subcutaneously twice weekly. The patient is instructed to

*Obtained from Don Baxter, Incorporated, Glendale, Calif.

take two drops of 1:10,000 histamine phosphate sublingually twice daily.

Nicotinic Acid: Nicotinic acid tablets (50 mgs.) are prescribed 30 to 45 minutes before breakfast and before dinner. The dose is adjusted by the patient up to 200 or 300 mgs. until a definite flush is obtained. Frequently a flush is obtained by a smaller dose before breakfast than that required before dinner. It is important that this be administered on an empty stomach to insure rapid absorption and maximum effect. If tolerance develops, the dose may be increased, or Roniacol may be substituted. Arlidin or Vasodilin has also been substituted on occasions.

Diet: A 2 Gm. salt diet of 1,800 calories is recommended. Coffee is not allowed because of the vasoconstrictor action of caffeine.

Sedation: An "autonomic stabilizer" such as Donnatol, Probanthine with Dartal, or Bellergal is frequently recommended. A tranquilizer or ataraxic may also be indicated.

Miscellaneous: Vitamin C, usually in the form of C.V.P., is prescribed in doses of 300 mgs. daily. Merazine is advised for vertigo if indicated. Cytamel or thyroid is administered if hypothyroidism is present.

SUDDEN SENSORY-NEURAL HEARING LOSSES.

In this report sudden sensory-neural hearing losses have included all cases in which a hearing impairment of an inner ear or neural type has developed in a period of one week or less in an otherwise healthy individual who has not received ototoxic drugs recently. The majority of losses in this series developed in a matter of hours. The only cases excluded are those that have fluctuated following the development of the sudden loss. These cases will be considered later.

This group comprises 223 patients, the majority of whom were seen in the last five years. In the last two years, approximately 2 per cent of our new patients have had this diagnosis made. Thirteen patients developed a loss in both ears. Nine of these had a simultaneous bilateral loss and

four developed a loss in the second ear from three months to 20 years following the first episode.

Age and Sex Distribution: The youngest patient in this series was 15 years old and the oldest was 84. Table I shows that there was a fairly even distribution of patients in the fourth, fifth, sixth, and seventh decades. Seventy-five per cent of the patients were over the age of 40. There were 35 per cent more females than males.

Type and Extent of Hearing Loss: Hearing losses were classified into four groups: low tone, flat, high tone, and

TABLE I.

Sudden Sensory-Neural Hearing Loss.

Age and Sex Distribution (N-223).

Age	Number	Per Cent		
10-19	5	2		
20-29	13	6		
30-39	39	17		
40-49	58	26	52 Per Cent	75 Per Cent over 40
50-59	57	26		
60-69	41	18		
70+	10	5		
Sex—				
Female	129	58		
Male	94	42		

total hearing loss. A hearing loss was considered to be a *low tone* if normal hearing was maintained at 4,000 or 8,000 c/s, or if there was a low tone tilt to the audiogram with a difference of 25 decibels between the frequencies 500 and 4,000 c/s. The hearing loss was considered to be low tone even if there was involvement of the high tones, if this high tone loss was also present in the other (normal) ear. The hearing loss was classified as *high tone* if normal hearing was maintained at 250 or 500 c/s or if there was a high tone tilt to the audiogram with a difference of 25 decibels between the frequencies 500 and 4,000 c/s. Any loss not falling into one of these two categories was considered to be a *flat loss* as long as the average loss in the speech hearing frequencies (500 through 2,000 c/s) did not exceed 90 to 95 decibels. If

the loss exceeded this, it was considered to be a *total loss* of hearing.

A flat type hearing loss occurred in 41 per cent of the 236 ears (see Table II). The next most common type was the high tone loss. Over 70 per cent of the group had an average hearing level or 50 db or more in the three speech hearing frequencies.

TABLE II.

Sudden Sensory-Neural Hearing Loss.

Type and Extent of Loss (N-236 Ears).

Type Loss	Number	Per Cent	Hearing Level (db) (500-2,000 c/s) 15-25 Per Cent	30-45 Per Cent	50-75 Per Cent	80+ Per Cent
Low Tone	39	17	13	41	46	
Flat	98	41	6	32	45	17
High Tone	69	29	1	17	65	17
Total	30	13				100

TABLE III.

Sudden Sensory-Neural Hearing Loss.

Tinnitus (N-223).

Present	86 Per Cent		
Type Specified—78 Cases			
Buzz	26	33 Per Cent	90 Per Cent Low Tone
Roar	23	29 Per Cent	
Low (Below 512 c/s)	16	21 Per Cent	
Rumble	3		
Hum	2		
Ring, Steam, Hiss	8		

Tinnitus: Eighty-six per cent of the patients complained of tinnitus (see Table III). This was usually a low tone tinnitus, the two most common types being buzzing and roaring. This may be compared to a study[18] of normal and hard-of-hearing individuals where low tone tinnitus was present in less than 40 per cent of those complaining of tinnitus.

Vertigo: Vertigo was present in 37 per cent of this group (see Table IV), and was most frequently of the induced or postural type. It occurred least frequently in those individuals with a low tone type of impairment and most frequently in

the group with flat and total hearing losses. Vertigo was more than twice as common in the females.

When spontaneous vertigo was present, it invariably occurred at the onset of the sudden hearing loss. In no case did the spontaneous vertigo have its onset after 48 hours and only in an occasional individual was there spontaneous vertigo prior to the onset of the loss. Although some had only a brief episode of spontaneous vertigo, the dizziness usually lasted from a few hours to three days, often requiring confinement to bed.

TABLE IV.

Sudden Sensory-Neural Hearing Loss.

Vertigo (N-223).		
Present	83	37 Per Cent
Type—		
Spontaneous		45 Per Cent
Induced		61 Per Cent
Occurrence of Vertigo Re Hearing Loss—		
Low Tone		20 Per Cent
Flat		44 Per Cent
High Tone		32 Per Cent
Total		47 Per Cent

Induced vertigo, when present, was not usually associated with an initial episode of spontaneous vertigo. As opposed to the spontaneous vertigo, the postural vertigo at times had its onset three or four days after the onset of hearing loss and often persisted for periods of weeks or months. In many cases it was the persistence of this postural vertigo that led the patient to seek medical advice five or six months following the onset of the hearing loss.

Vestibular function tests were performed on 20 patients. Thirteen of these had normal responses and of this group, 11 had losses greater than 50 decibels. Of the four who had no vestibular response, all had losses in excess of 75 decibels.

Radiographic Findings: Approximately one-third of the patients had radiographic examinations of the temporal bone. Of 92 patients seen in 1958 and 1959, 17 were X-rayed by Eugene Compere, M.D. One of these (a case of clinical oto-

sclerosis) had diffuse otic capsule otosclerosis. Nine patients had petrosal sclerosis, and seven showed a normal radiographic picture. A large percentage of individuals with progressive *hereditary* types of sensory-neural hearing loss show petrosal sclerosis, and this may also be true in the sudden losses. At the present time, X-rays are being obtained in most cases of hereditary and sudden sensory-neural hearing losses to investigate this finding further.

Summary: Sudden non-fluctuating sensory-neural hearing losses in otherwise healthy individuals usually occur over the age of 40, and are more common in the female. The loss often involves all of the frequencies resulting in a flat or high tone

TABLE V.

Sudden Sensory-Neural Hearing Loss.

Onset of Treatment Re Recovery.			
Treated	Number	Recovered	Per Cent
Total	70	24	34
Within Four Days	21	13	62
Within Two Weeks	38	20	53
Within Six Weeks	49	23	47
After Six Weeks	21	1	5

type of curve with an average loss in the speech hearing frequencies of 50 decibels or more. A low tone tinnitus is the rule, and vertigo is present in about one-third of the cases.

TREATMENT RESULTS—SUDDEN LOSSES.

A vasodilator regime was prescribed for 66 patients (70 ears). Seven were treated one year or more following the onset of a sudden loss. Five of these were treated because of persistent postural vertigo and annoying tinnitus. In all cases the response to treatment was satisfactory although there was no change in the hearing level. In the other two cases (15 and 20 years following the hearing loss) treatment was instituted in connection with a second ear that had become involved by a sudden hearing loss recently.

In the following paragraphs and accompanying tables an ear was considered to have recovered if the hearing returned

to a 15 decibel level or better, if the hearing returned to the level of the opposite ear, or (in a few cases with severe hearing loss) if the hearing returned to a serviceable level.

Twenty-four of the 70 treated cases recovered (see Table V). Of those treated within four days of the onset of loss, 62 per cent recovered. Forty-seven per cent of those treated within six weeks recovered, but only one case treated after six weeks returned to normal. Details of the recovered cases are shown in Table VI.

Age and Sex Distribution: Table VII shows the age and sex distribution of individuals treated within six weeks who recovered. Fifty-five per cent of those between the age of 30 and 59 recovered. Under 30 and over 60 the results were poor. There was no significant difference between the recovery rate in females and males.

Type and Extent of Hearing Loss (See Table VIII): In the group of cases treated within six weeks, the distribution relative to type and extent of loss is approximately the same as that in the 223 cases. There was no apparent selective factor from this standpoint. Of 12 individuals with a low tone loss, ten recovered. The flat and high tone losses showed a much lower recovery rate, and the total loss cases showed the poorest results. Eleven of 16 cases having a loss of 45 decibels or less recovered. Favorable factors appear to be the presence of a tow tone loss and an impairment of 45 db or less.

Tinnitus: There was no apparent relationship between the presence or character of the tinnitus and the incidence of recovery.

Vertigo: Vertigo was present in a third of the 223 patients. This same incidence was present in the treated group and in the group of cases treated within six weeks of the onset of their hearing loss. There was no apparent selective factor from the standpoint of vertigo. Despite this lack of selection, only two cases of 24 (8 per cent) that recovered had vertigo at any time during the course of their illness (see Table IX). The absence of vertigo appears to be favorable for recovery.

Recovery Time: Eighteen cases were treated within one

TABLE VI.

No. Case	Age	Sex	Hearing Loss				Tinnitus	Vertigo	Therapy		
			Curve	Level (Avg. 500-2,000)	Onset	Fluctuation			Onset	Type	Response
2	32	F	LT	25	S	—	+	—	1 day	+	Normal hearing 3 weeks, maintained 3 years.
45	47	F	F	60	S	—	+	I	1 week	+	Level of other ear (20 db) 1 month; maintained at 1 year.
46	43	F	LT	40	S	—	—	—	1 week	+	15 db at 2 months, 5 db at 2 years.
47	51	F	LT	35	W	—	+	—	1 month	M	13 db at 2 months, 25 db at 1 year. No change 3 years.
71	64	F	LT	35	S	—	+	—	6 weeks	+	Normal at 4 months. Maintained at 1 year.
88	34	M	F	65	S	—	Buzz	—	2 days	+	7 db at 9 days.
89	49	M	HT	75	S	—	Buzz	—	1 week	+	Normal at 2 weeks.
99	38	M	LT	70	S	—	Hum	—	3 days	+	Normal 1 week, maintained 1 year.
110	41	M	F	60	S	—	Buzz	—	1 day	+	Normal 4 days, maintained 1½ years.
122	44	F	F	80	S	—	—	—	4 days	+	Level of other ear (10 db) at 1 month.
129	69	M	F	90	S	—	Roar	—	5 days	+	12 db at 7 days, maintained 1 year.

134	35	M	LT	15	S	—	+	—	3 days	+	Minus 5 db in 1 week.
140	50	M	F	45	S	—	Roar and Buzz	—	2 weeks	+	Normal 10 days, maintained 1 year.
164	46	M	HT	30	S	—	Steam	S	2 weeks	+	15 db at 1 month, 8 db at 4 months.
169	35	F	HT	75	S	—	—	—	2 days	+	Normal at 1 month.
175	31	M	F	60	S	—	+	—	6 months	+	35 db at 1½ months, normal 4 months.
183	47	M	T	—	S	—	+	—	20 years	+	No response.
			F	45	S	—	+	—	5 weeks	+	27 db at 4 months, maintained 2 years.
193	59	F	F	70	S	—	+	—	1 week	M	Normal at 2 weeks.
203	43	M	LT	70	S	—	Steam	—	2 days	+	22 db at 6 weeks, 7 db at 6 months, maintained 2 years.
213	49	M	LT	70	D	—	+	—	4 days	+	Normal at 2 weeks.
219	40	F	HT	40	S	—	Ring	—	1 day	+	"Normal" at 1 week.
221	53	F	LT	30	S	—	Low	—	1 day	+	Normal at 1 month.
224	57	M	T	—	S	—	Buzz	—	3 days	+	28 db at 2 weeks. (On Dicumerol and Priscoline at time of loss).
228	54	F	LT	30	S	—	—	—	1 day	+	Normal 1 day. Maintained 3 months.
			F	30	S	—	—	—	4 years	+	No change.

Case No.	Age	Sex	Hearing Loss: Curve	Level (Avg. 500-2,000)	Onset	Fluctuation	Tinnitus	Vertigo	Therapy: Onset	Type	Response
1	39	M	LT	40	G	—	Buzz	—	6 months	+	12 db at 1 month; maintained.
			LT	40	G	—	Buzz	—	6 months	+	22 db at 1 month, then fluctuated.
9	55	M	LT	40	G	+	Low	—	8 months	+	Normal at 2 months, then fluctuation.
			LT	45	D	—	Low	I	1 week	+	Normal at 2 weeks, maintained 1 year.
15	57	M	LT	20	D	+	+	—	5 weeks	+	Normal at 3 days, fluctuated for months.
16	58	M	LT	45	S	+	Low	—	2 weeks	+	Fluctuated to normal with treatment.
18	51	F	LT	30	G	—	Buzz	—	1 year	+	Normal at 2 months, maintained at 8 months.
19	54	M	LT	45	S	+	+	—	2 months	+	11 db at 1 month.
20	71	F	LT+HT	15	G	+	Roar	—	3 months	M	Normal at 3 weeks.
26	13	F	T	—	S	+	Buzz	—	1 week	+	Normal after treatment. See Summary.

Curve: LT—Low Tone; F—Flat Loss; HT—High Tone; T—Total Loss.

Onset: S—Sudden; D—1 day; W—1 week or less; G—Gradual.

Vertigo: I—Induced; S—Spontaneous.

Therapy: +—Full Vasodilator Regime; M—Modified Regime (Minus IV Histamine).

week of the onset of a sudden hearing loss. Six of these cases recovered within a week, and these were the only cases that recovered within one week of onset of therapy. Other than this, there seems to be no definite correlation between the time of onset of therapy and the speed of recovery. Eighty-five per cent of the group that did recover their hearing, did

TABLE VII.

Sudden Sensory-Neural Hearing Loss.
Cases Treated Within Six Weeks (N-49).

Age and Sex Distribution.	Recovered	Per Cent	
Age—			
Under 30	0(3)	0	
30-39	5(10)	50	
40-49	10(15)	67	21(38)—55 Per Cent
50-59	6(13)	46	
Over 60	2(8)	20	
Sex—			
Female	11(24)	46	
Male	13(25)	52	

TABLE VIII.

Sudden Sensory-Neural Hearing Loss.
Cases Treated Within Six Weeks (N-49).

Type and Extent of Loss.	Recovered	Per Cent
Type Loss—		
Low Tone	10 (12)	83
Flat Loss	8 (19)	42
High Tone	4 (10)	40
Total Loss	1 (8)	12
Extent Loss (500-2,000 c/s)—		
15-45 db	11 (16)	69
50-75 db	9 (18)	50
80 db+	3 (15)	20

so within a period of six weeks from the onset of therapy (see Table X). Those who had not recovered by six weeks had shown evidence of response to treatment: partial hearing improvement, fluctuation in hearing, or marked fluctuation in tinnitus.

Treatment After Six Weeks: Cases treated six weeks or more following the onset of a sudden hearing loss, but within

one year of the loss, were analyzed to see if there was some factor other than time that could be related to the lack of response. Analyzing this group from the standpoint of age, type and extent of loss and incidence of vertigo revealed no significant difference from the group of cases treated under six weeks or from the overall group of treated cases. It would seem that time was the major factor in the failure of these cases to respond to therapy.

Summary: Intensive vasodilator therapy resulted in recovery of hearing in approximately 50 per cent of the cases

TABLE IX.

Sudden Sensory-Neural Hearing Loss.

Response to Treatment Re Vertigo.

Total Cases Treated Within Six Weeks	49	
With Vertigo	15	(31 Per Cent)
Number of Cases That Recovered	24	
With Vertigo	2	(8 Per Cent)

TABLE X.

Sudden Sensory-Neural Hearing Loss.
Recovered Cases (N-24).

Recovery Time	No. Cases	
Less Than Two Weeks	11	85 Per Cent Within Six Weeks
Two to Four Weeks	7	
Four to Six Weeks	2	
Six Weeks to Four Months	4	

of sudden non-fluctuating sensory-neural hearing losses treated within six weeks of the onset of the loss. It appears that time is a major factor in the failure of cases treated later than six weeks to respond to treatment. Low tone impairments respond more favorably than others, as do impairments of less than 50 decibels. The presence of vertigo appears to be a poor prognostic sign.

FLUCTUATING AND GRADUAL SENSORY-NEURAL HEARING LOSSES.

This group consists of 24 patients, three of whom had bilateral hearing loss, two of these occurring simultaneously. This group includes fluctuating sensory-neural hearing losses

of sudden or gradual onset, and gradual non-fluctuating losses in which vasodilator therapy was used. Most of these patients were treated within the last two years.

Age and Sex Distribution: Table XI demonstrates that the distribution of cases is similar to that seen in the sudden loss group. Seventy-nine per cent of the individuals were over the age of 40. There was an equal distribution between the sexes.

TABLE XI.

Fluctuating and Gradual Sensory-Neural Hearing Losses.

Age and Sex Distribution (N-24).	No. Cases	Per Cent	
Age—			
Under 30	1	4	
30-39	4	17	
40-49	2	8	79 Per Cent Over 40
50-59	10	42	
60-69	6	25	
70+	1	4	
Sex—			
Equal Distribution.			

TABLE XII.

Fluctuating and Gradual Sensory-Neural Hearing Losses.

Type and Extent of Loss (N-27 Ears).			Hearing Level (db) (500-2,000 c/s)			
Type Loss	No. Cases	Per Cent	15-25	30-45	50-75	80 +
Low Tone	23	85	9	11	3	–
Flat	2	7.5	–	–	2	–
High Tone	0		–	–	–	–
Total	2	7.5	–	–	–	2

Type and Extent of Loss: Cases were grouped into four categories (low tone, flat, high tone, total hearing loss), using the same criteria as for the sudden loss group. Eighty-five per cent showed a low-tone type of hearing impairment (see Table XII). No high tone losses were observed. The majority of cases had less than a 50 decibel hearing loss.

Tinnitus: Tinnitus was present in all but one case (see Table XIII), and was of the low tone type.

Vertigo: Seven patients (30 per cent) had had vertigo at

some time during their illness. In only one of these patients was the vertigo spontaneous, and this for a period of approximately five minutes at the onset of a sudden low tone hearing loss.

Radiographic Findings: Eight patients had X-ray examinations by Dr. Compere. One of these showed diffuse otic capsule otosclerosis. Four patients had petrosal sclerosis, and in three the X-ray showed normal findings.

TABLE XIII.

Fluctuating and Gradual Sensory-Neural Hearing Losses.

Tinnitus (N-24).		
Present	23—95 Per Cent	
Type Specified—16 Cases		
Buzz	6	100 Per Cent Low Tone
Roar	5	
Low Tone (Below 512 c/s)	5	

TABLE XIV.

Fluctuating and Gradual Sensory-Neural Hearing Losses.
Treated Cases (N-15 Ears).

Recovery Rate and Type of Loss.			
Recovered		No.	Per Cent
Total		10 (15)	67
Treated Within Six Weeks		4 (7)	57
Type Loss	No.	Recovered	Per Cent
Low Tone	13	9	69
Total Loss	2	1	50

Summary: Fluctuating and gradual sensory-neural hearing losses occur most commonly over the age of 40. The loss usually involved the low tones more than the high tones, with an average loss in the speech hearing frequencies of less than 50 decibels. A low tone tinnitus is the rule. Spontaneous vertigo is uncommon.

TREATMENT RESULTS—FLUCTUATING AND GRADUAL LOSSES.

There were 13 patients (15 ears) who were placed on a vasodilator regime. Of this number, ten ears recovered (see Table XIV). Time of onset of therapy did not seem to be an

important factor. Nine of 13 cases with low tone hearing loss recovered. Details of the recovered cases are shown in Table VI.

Age and Sex Distribution: There are too few cases in this series to draw any conclusions, but it is interesting that five of six cases in the age group 50 to 59 recovered. There were nine males, of whom five responded, and four females, of whom three responded.

Vertigo: Vertigo was present in two of the 13 individuals treated. Of the eight who recovered, one had vertigo.

TABLE XV.

Fluctuating and Gradual Sensory-Neural Hearing Losses. Recovered Cases (N-10).

Recovery Time and Duration of Loss.	No.	Per Cent
Recovery Time—		
Within Two Weeks	5	50
Within Four Weeks	9	90
Duration of Loss Before Treatment—		
One Year	1	
Eight Months	1	
Six Months	1	

Recovery Time: Five of the ten ears that recovered did so within two weeks (see Table XV). Four more recovered during the following two weeks, and the final case had shown maximum response at two months. It is interesting, particularly in comparison with the findings in cases of a sudden *non-fluctuating* loss, that one case responded after a loss had been present one year, one after eight months, and one after six months. It appears that the time factor in treatment of fluctuating losses is not critical as long as the hearing continues to fluctuate.

Summary: Intensive vasodilator treatment resulted in recovery of hearing in approximately two-thirds of the cases of fluctuating and gradual sensory-neural hearing losses. The length of time between onset of loss and onset of treatment was not a factor in this recovery.

CASE REPORTS.

A summary of each of the 37 recovered cases is presented in Table VI. The following cases are presented in more detail to demonstrate certain interesting aspects of the history or treatment. The case numbers correspond to those in Table VI.

Case 110. This demonstrates optimum response in an individual treated within a few hours of onset of a sudden sensory-neural hearing loss.

A 41-year-old physician developed buzzing in his right ear while performing emergency surgery one evening. The following morning he awakened with a severe hearing loss in that ear. There was no vertigo. Examination a few hours after the onset of the hearing loss revealed a

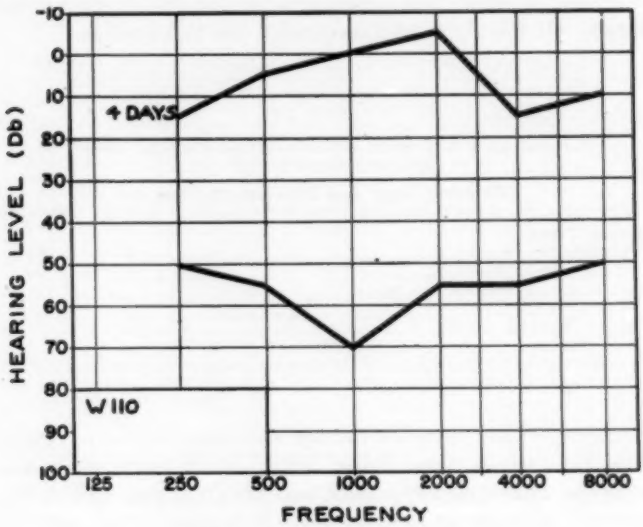

Fig. 1. Case 110: Sudden Loss.

60 decibel level in the right ear and normal hearing in the left ear. A vasodilator regime was instituted and an examination four days later demonstrated normal hearing (see Fig. 1). A year and one-half later hearing tests showed normal hearing.

Case 129. This demonstrates an excellent response in an elderly individual with a profound hearing loss of a flat type. Statistically he should have had very little chance of recovery.

A 69-year-old man developed a full feeling in his left ear associated with roaring tinnitus and marked hearing loss five days prior to examination. There was no vertigo. Examination revealed normal hearing in the right ear and a 90 decibel hearing level in the left ear. A vasodilator regime was instituted. Within seven days the roaring noise had subsided, and he said his hearing had returned to normal. An audiogram

made three weeks after the initial examination demonstrated a 12 decibel hearing level (see Fig. 2). Normal hearing was maintained during a one-year follow-up period.

Case 20. A high and low tone loss developed simultaneously in this elderly patient. Minimal therapy resulted in recovery of hearing and relief of tinnitus despite the fact that the symptoms had been present for three months prior to treatment.

A 71-year-old woman was examined because of a roaring tinnitus in the left ear. The tinnitus had developed following eye surgery some three

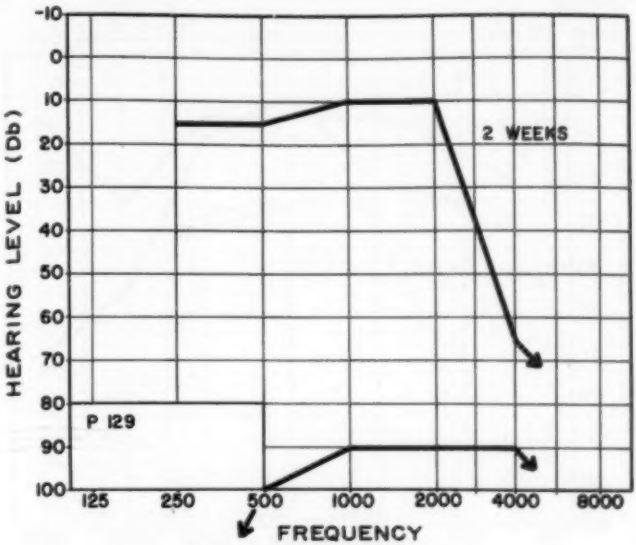

Fig. 2. Case 129: Sudden Loss.

months prior to this examination. The tinnitus and stuffiness in her left ear fluctuated. There was no vertigo.

Examination revealed a combined high and low tone hearing loss with normal hearing at 1,000 c/s. Sublingual histamine, nicotinic acid, and Vitamin C were recommended. Three weeks later examination revealed marked improvement in hearing and a remission of all symptoms (see Fig. 3).

Case 219. A high tone dip may be reversible as demonstrated in this patient upon whom we had audiograms prior to the hearing loss.

This 40-year-old woman was first examined because of a seven-year history of a gradually progressive hearing loss associated with tinnitus. Examination revealed a conductive hearing impairment of 48 decibels in the right ear and 23 decibels in the left ear. Right stapes mobilization improved the hearing to a 25 decibel level.

Two months following mobilization she developed a sudden ringing tinnitus and stuffiness in the *unoperated* ear. An audiogram made at that time demonstrated a sharp tonal dip at 2,000 and 4,000 c/s in the left ear. A vasodilator regime was instituted and a partial hearing improvement was noted immediately following the first intravenous histamine. Her hearing had returned in one week (see Fig. 4).

Case 1. A gradually progressive bilateral non-fluctuating hearing loss was present for six months. The only key to the possibility that this might be of vascular origin and possibly reversible was the presence of a low pitched buzzing tinnitus.

A 39-year-old man stated that he had noticed a buzzing tinnitus in his

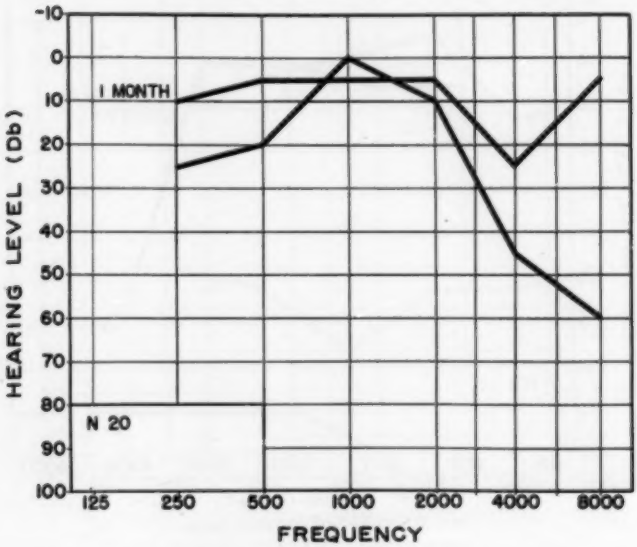

Fig. 3. Case 20: Fluctuating High and Low Tone Loss.

left ear for six months before being seen and that his right ear became involved one month later. During these six months his hearing had gradually decreased to a point where he had lost his job and purchased a hearing aid. There was no history of ototoxic drug therapy and no vertigo.

An audiogram demonstrated a 40 decibel hearing level in each ear. A vasodilator regime was instituted. During the next three or four weeks his hearing gradually returned. Fluctuating tinnitus was noticed. Audiometric examination after one month of therapy revealed a 12 decibel level in the right ear (see Fig. 5) and a 22 decibel level in the left ear (see Fig. 6). Therapy was continued and two months later the hearing level in the right ear was unchanged; the left ear fluctuated.

Case 9. This patient had a bilateral hearing impairment, gradual in one ear (eight months' duration) and a recent sudden loss in the other ear. The ear with the sudden loss responded immediately to treatment. Because of the tinnitus and hearing level fluctuation in the other ear, treatment was continued with gradual improvement to a serviceable level.

A 55-year-old man was seen regarding a hearing aid. Eight months previously he had noted a gradual onset of fluctuating hearing loss in his left ear associated with low-pitched tinnitus and stuffiness in the ear. His hearing level had stabilized during the previous three or four

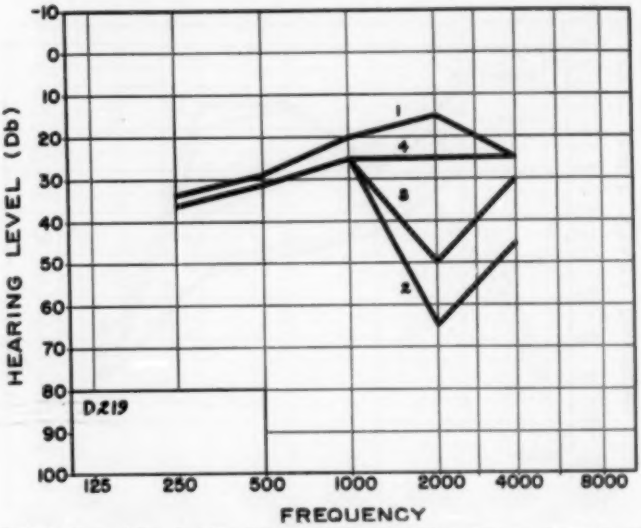

Fig. 4. Case 219: Sudden Loss. 1. Two months prior to loss; 2. one day after onset of loss; 3. after first i.v. histamine; 4. after one week of treatment.

months. One week before examination he had noticed a stuffy sensation with roaring tinnitus in his right ear. He had noticed mild unsteadiness for one day prior to his first visit. Examination revealed a bilateral sensory-neural hearing impairment of 40 decibels in the right ear and 45 decibels in the left ear.

A vasodilator regime was instituted. The hearing in the most recently affected ear returned to a normal level within 12 days, and this has been maintained for one year (see Fig. 7). Hearing in his left ear improved only slightly and then regressed. Because both the hearing level and the tinnitus in the left ear were fluctuating, treatment was continued. An audiogram at two months revealed an 8-decibel level (see Fig. 8). The hearing in this ear continues to fluctuate particularly if histamine therapy is omitted.

Case 26. This is the youngest patient in the series. The case is presented because it shows repeated dramatic response to intravenous histamine therapy.

This girl was first seen in 1955 at the age of nine. A hearing loss had been discovered at the age of four and there had been no change since that time. An audiogram revealed residual hearing, only, at 256 and 512 c/s in the right ear. The left ear showed a mixed loss of 70 decibels, predominantly sensory-neural except in the low frequencies. A hearing aid was advised and accepted. She was seen intermittently during the following four years.

In April, 1959, (at the age of 13) she developed a sudden buzzing and

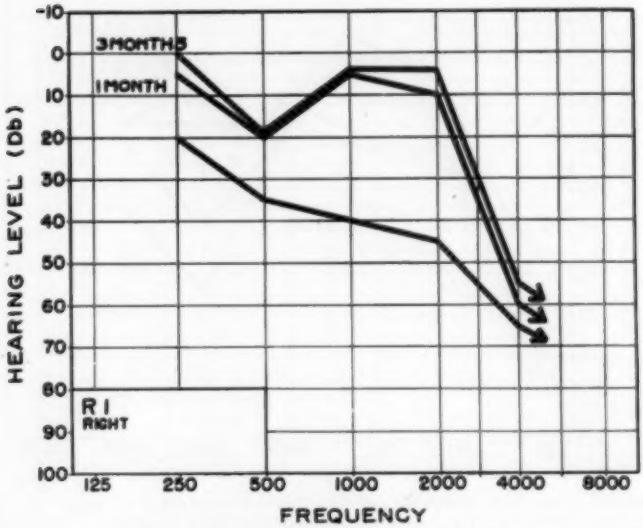

Fig. 5. Case 1: Gradual Loss, Right Ear.

hearing loss in her left ear. There was no dizziness. Examination one week later revealed an average hearing level of 100 decibels in the left ear.

She was immediately given intravenous histamine. During the course of the first i.v. her hearing returned to the point where she could use her hearing aid again. For the next two days, her hearing fluctuated slightly. Three weeks later, an audiogram revealed a 55 decibel hearing level (see Fig. 9). Vasodilator therapy was continued.

During the following three months, she had two further episodes of sudden total hearing loss. Each attack responded immediately to intravenous histamine. Her hearing has stabilized at a satisfactory level up to the present time (about five months).

DISCUSSION.

Controls.

One of the major difficulties in evaluating the results of treatment in this group of cases is the lack of a control series. There is a natural hesitancy to withhold treatment when by so doing the patient may be left with a permanent severe sensory-neural hearing loss. Spontaneous recovery has been

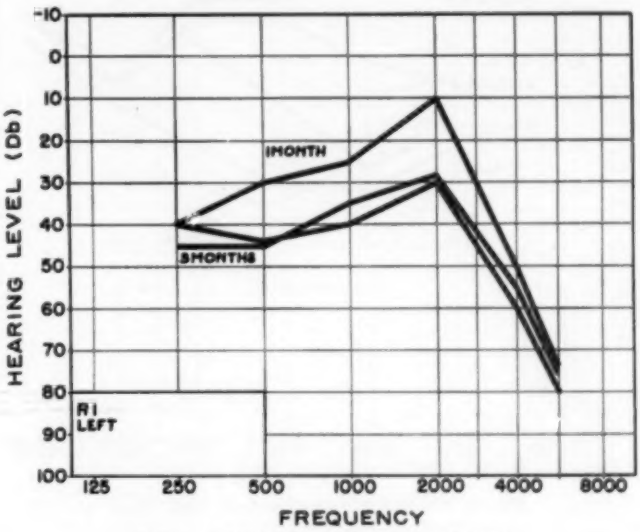

Fig. 6. Case 1: Gradual Loss, Left Ear.

noted by some[3a,3c,9,10,19] and perhaps a small percentage of the individuals in this series would have recovered without treatment. Certainly the pessimistic view taken by many otologists[1,2,3a,3b] would indicate relatively little likelihood of recovery in the majority of cases, with or without treatment.

A few reports have been found in which treatment was not instituted and adequate follow-up was obtained. Perhaps these reports could serve as a control for this series. Svane-Knudsen[4] reported 21 cases of sudden sensory-neural hearing

loss. Although a partial hearing improvement occurred in some cases, none showed return to normal hearing. All of his cases had a total or high tone type loss, and the majority had vertigo, both of which factors are unfavorable for recovery according to the results in the present series. He believed that a toxic or infectious neuronitis was the most likely cause in his cases.

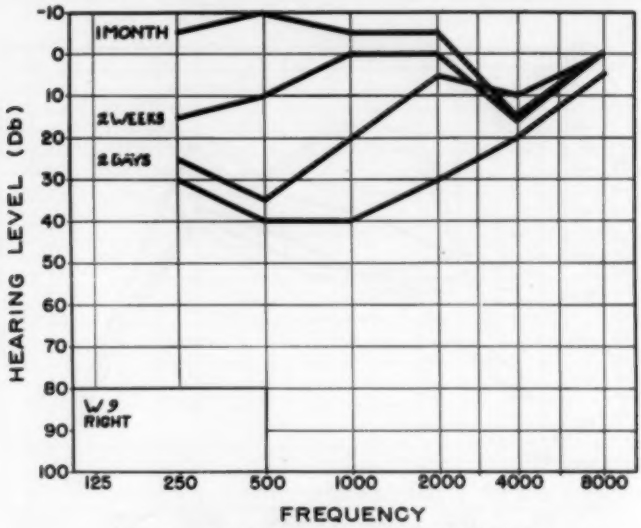

Fig. 7. Sudden Fluctuating Loss, Right Ear.

Rasmussen[5] stated that suddenly occurring unilateral deafness in otherwise normal individuals is a very rare phenomenon. He observed 18 cases in 15 years. Eleven of these had a profound deafness, and 15 had vertigo. The hearing level in only one patient returned to normal.

Error in Diagnosis.

The majority of patients observed were not seen within six weeks of the onset of their hearing loss. Many of these came for an examination a year or so later hoping that they were candidates for stapes mobilization. Others were pri-

marily concerned about the persistence of tinnitus or postural vertigo and had waited three or four months following a sudden hearing loss before consulting an otologist. A number of patients, however, were seen late because of an error in diagnosis. This is unfortunate because it is realized that up to 50 per cent of these patients might have had normal hearing had a correct diagnosis been made and vasodilator treatment instituted early. A mistaken diagnosis of a middle

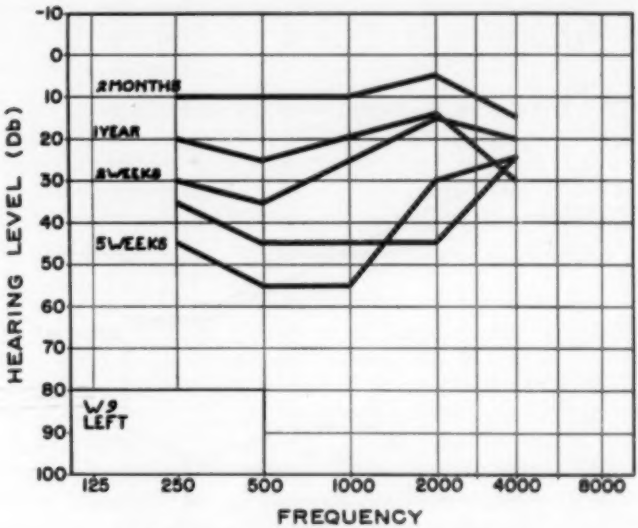

Fig. 8. Case 9: Gradual Loss, Left Ear.

ear impairment may have been made on a basis of history alone, inasmuch as the subjective complaints are quite similar to those of Eustachian tube blockage. There is a feeling of stuffiness, as though there were water in the ear, and often the patient will volunteer that this is "just like what happens when I come down from the mountains." The initial impression may be strengthened by the fact that a chronic vasomotor rhinitis may become more symptomatic at the time of the sudden sensory-neural hearing loss due to the fact that

both conditions are probably manifestations of autonomic dysfunction. Careful examination of the eardrum membrane, including use of the pneumatic otoscope, should suggest that the problem is not due to tubal blockage. In those cases of serous otitis media where the membrane appears almost normal, there is usually marked limitation of motion as demonstrated by the Valsalva maneuver and the pneumatic otoscope. An incorrect diagnosis of conductive hearing im-

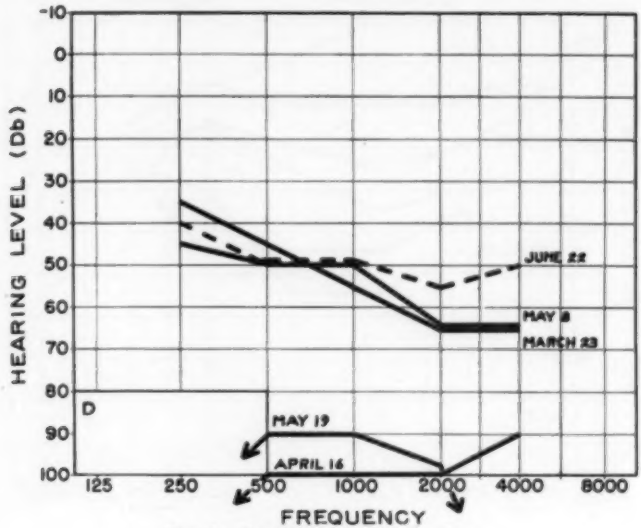

Fig. 9. Case 26: Fluctuating Loss.

pairment may also result from an audiogram in which the opposite (normal) ear has been inadequately masked, resulting in a shadow bone curve on the affected side.

Central Nervous System Disease.

When a diagnosis of a sudden unilateral sensory-neural hearing loss has been made, it is important to rule out central nervous system disease. At the initial visit the cranial nerves are carefully examined, paying particular attention to corneal and nasal vestibular sensation. At the present time X-rays

of the petrous pyramid are obtained routinely in all these cases. If neurological and radiological examinations are negative, a vestibular test is deferred pending the outcome of vasodilator treatment. If there is no response to treatment within six weeks, a vestibular test is then carried out. Should this test reveal a dead labyrinth, a spinal fluid protein examination is obtained, even though neurological examination is negative. If the patient is first examined two months or more after the onset of a sudden non-fluctuating loss, a vestibular test is performed at the initial examination, inasmuch as vasodilator therapy will in all probability not be instituted.

Three cases of posterior fossa pathology presented as sudden sensory-neural hearing loss. Two of these had acoustic neuromata, and in each case the neuroma was over 50 per cent cystic, apparently the result of a hemorrhage. The other case had a thrombosis of a vessel supplying the brain stem with mild sensory and motor signs when first examined.

Vasodilator Therapy.

Vasodilator therapy should be advised for any individual with a sudden sensory-neural hearing loss of obscure origin seen within six to eight weeks of onset. If seen after two months, treatment is probably not indicated unless there has been fluctuation in the hearing. There is no time limit, however, for institution of therapy in *fluctuating* sensory-neural hearing impairments. A trial of vasodilator therapy is indicated in gradually progressive non-fluctuating sensory-neural hearing losses if a low pitched buzzing or roaring tinnitus is prominent. Two such cases are included, one treated after one year (Case 18, see Table VI) and one treated after six months (summary, Case 1).

Once vasodilator therapy has been initiated, how long should it be continued? Eighty-five per cent of the sensory-neural losses that responded did so within six weeks of onset of treatment. Those that had not recovered by this time had shown some evidence of recovery as manifested by partial improvement in hearing, fluctuation of hearing, or marked fluctuation of tinnitus. Based on these findings it would

seem that there is little point in continued therapy past six weeks unless some encouraging signs are shown.

When a non-fluctuating hearing loss has shown an immediate response to treatment (recovery within one to two weeks) medication may be gradually eliminated over a two-week period. If response to treatment has been gradual, and in the case of fluctuating and gradual losses, some form of vasodilator therapy (usually nicotinic acid and sublingual histamine) should be continued for a period of from one to two months after the hearing has returned.

CONCLUSIONS.

1. A sudden sensory-neural hearing loss is a medical emergency. Intensive vasodilator therapy should be initiated immediately, and has resulted in recovery of hearing in 47 per cent of the cases in this series.

2. Favorable prognostic signs in sudden sensory-neural hearing losses are the following:

a. Low tone type of impairment.

b. Forty-five decibel or less hearing level in the speech hearing frequencies.

c. Absence of vertigo.

If an individual with the above listed findings is treated within six weeks of onset of a sudden hearing loss, he should have better than a 50 per cent chance of recovery of serviceable hearing.

3. Fluctuating sensory-neural hearing losses are predominantly of the low tone type associated with a low pitched tinnitus. Intensive vasodilator therapy has resulted in recovery of hearing in two-thirds of the cases in this series.

4. Gradually progressive non-fluctuating sensory-neural hearing losses associated with a low pitched buzzing or roaring tinnitus, should be given the benefit of intensive vasodilator therapy. An occasional case may respond to this treatment.

SUMMARY.

The clinical findings in 247 patients with sudden and fluctuating sensory-neural hearing losses are presented. A vasodilator regime is outlined and was instituted in 79 of these patients. The results of this treatment are presented.

Although no conclusions have been drawn as to the etiology in these cases, treatment based on the assumption that vascular spasm is fundamental in their development has resulted in recovery of hearing in approximately 50 per cent of the cases treated within six weeks of onset of the loss.

ACKNOWLEDGMENT.

The author thanks Aram Glorig, M.D., for his advice in the preparation of the statistical tables.

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A "Short Course in Audiology" is offered several times each year by the Section of Audiology, Department of Otorhinology, Temple University School of Medicine, Philadelphia 40, Pa.

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For further information write Philip E. Rosenberg, Ph.D., Director, Section of Audiology, Temple University Medical Center, 3401 North Broad St., Philadelphia, Pa.

VARIATIONS OF RESULTS IN TREATMENT OF POSTOPERATIVE EAR INFECTIONS.*

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(By Invitation),
MARSHALL H. HOOD, M.D.,
and
CHARLES S. SALE, M.D.,
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This report concerns mixed infections of the postoperative ear and has been adapted from the original and as yet unconfirmed clinical observations of one of us (M. H. H.).

The incidence of mixed infection, which includes pseudomonas during or at the end of the postoperative phase of an otherwise faultlessly managed otologic operation, is one of the most exasperating and challenging facets in otolaryngologic practice.

When an otologic procedure is planned, the surgeon must assume that he can control all the important variables from the necessarily rigid asepsis, to the successful psychic guidance of the patient through preoperative, operative, postoperative and the initial part of the after care phase; however, as the postoperative stage passes, and the packing is gradually removed, the healing process brings back the perception of sensation, including that of itching, and the danger of conscious or unconscious finger exploration by the patient becomes apparent.

The impressive ceremony of sterile dressings, and the litany mass reiteration by the physician and his aides to avoid injury to the ear may persuade most patients to cooperate until final healing is completed; but there are some who do

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not cooperate. These are the patients with a long-standing history of intermittent drainage, who have been fingering their ears unconsciously, as long. This patient may take a perverse joy in converting the initial period of the after care phase into an exercise in the management of external otitis.

In the occasional case, completely innocent professional cleansing of an old radical cavity will stir up old infection. When this type of disease is complicated by the introduction of fungus spores, the resulting growth in the depth of the cavity will defy successful cure. It was the reference of just such a case of aspergillus niger, which led me to the treatment advocated by Marshall Hood, who has been successfully relieving such cases for over 20 years with 6 per cent sulphurous acid.

Sulphorus acid, H_2SO_3, is made by combining sulphorous anhydride with water. It is volatile, unstable, has a rather unpleasant and distinctive smell, and is said by our patients to cause a burning sensation to an inflamed otic skin, as does vinegar or alcohol. A chemical firm in our locality, the Virginia Smelting Company, graciously furnishes us with our material. By keeping the stock bottle under refrigeration and taking out only 5-10 cc. at a time, we are able to retain the virility for approximately three months.

Currently the listed authors are engaged in a cooperative project, whose purpose is to confirm by a controlled scientific approach, the clinical observations of our senior member. The cases listed below have been drawn from my personal series and are presented to show essentially safe, effective control experienced in relieving the occasional local secondary infection which jeopardizes plastic procedures of the ear. In the recalcitrant patient, the discovery of the characteristic smell found on the offending finger, after the initial treatment, emphasizes the importance of avoidance, and the implied threat of more pain if further irritation from self-trauma occurs, insures continued cooperation of the patient.

Case 1. Mrs. D. N., 25-year-old, white, female, choir director who was referred after exhaustion of the treatment resources of the physician, who had innocently irrigated a three-year-old radical cavity, was first seen on November 13, 1958, and last seen on February 24, 1959. During weekly

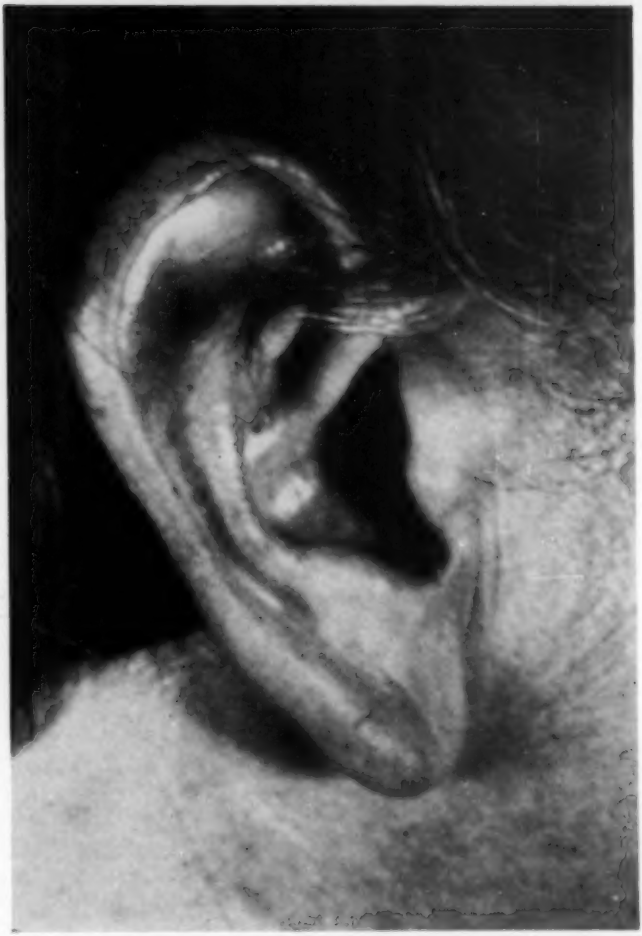

Fig. 1.

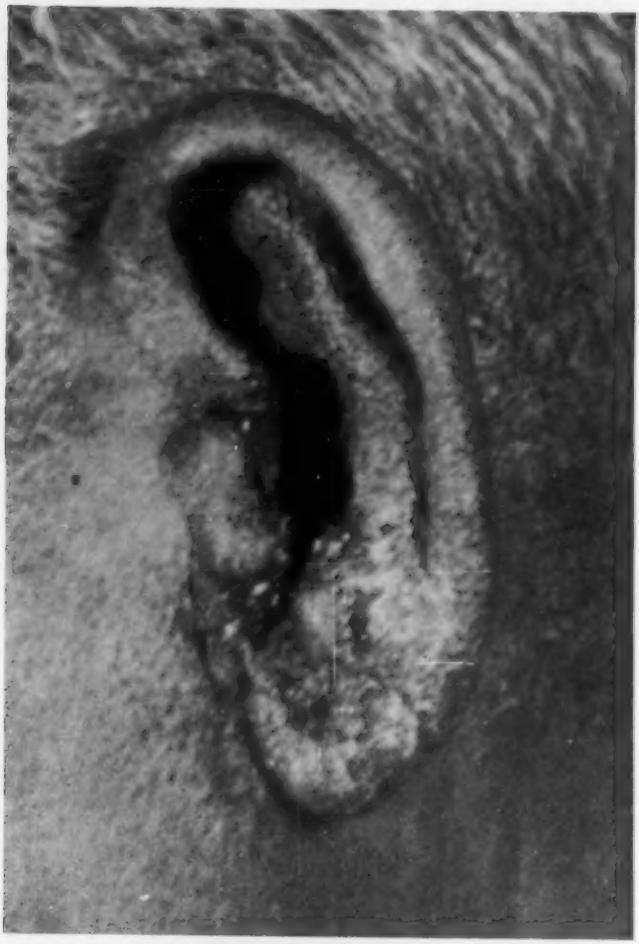

Fig. 2.

visits in November and December, the mixed infection was attacked with most of the standard varieties of treatment, with riddance of the staph. albus, and a prompt increase of the aspergillus niger. Consultation with Dr. Hood was sought early in January, and his method of meticulous cleansing, followed by thorough scrubbing of every nook and cranny with acid-soaked swabs, was done on January 10, 1959. The immediate subjective relief and the improved appearance on the visit of January 13, gave us new hope, and after three such visits, it became apparent that while the sinodural angle and the mastoid tip undercuts were still growing fungi, we were ahead. In our elation, the patient permitted me to fill the cavity with a newly prepared solution and demonstrated the courage to

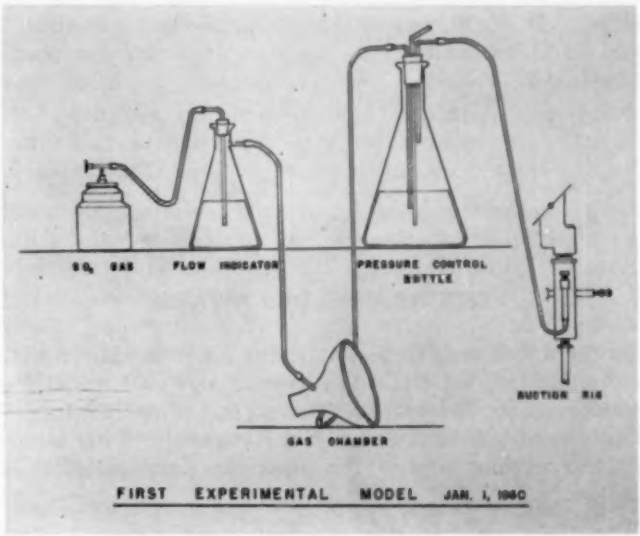

Fig. 3.

permit it to remain for four minutes. This was extended to ten minutes one week later, and the patient was discharged on February 24, 1959.

Case 2. Mrs. G. J., white, housewife had a modified radical mastoidectomy with skin graft on October 12, 1959. Three days before her discharge from the hospital, on October 20, she got her hands under the bandage and scratched the donor site and the ear canal vigorously. The packing still present in the ear protected the ear drum area, but the self-inflicted trauma continued to appear in spite of the exhortations of the physician and her family.

The case had been designated as a control, was followed carefully, with scrupulous cleanliness, neomycin ointment and powder to the plastic areas, and office visits every four to seven days. The depths of the cavity

were carefully walled off until culture taken from the tip area indicated a mixed infection of staphylococcus aureus, B. coli and pseudomonas on November 20. The routine was changed to the acid pattern on December 1, 1959, and on December 12, 1959, all the surface granulation tissue had disappeared, and by Decemeber 24, the ear was dry. There were breaks in the skin, and the acid drops routine was continued, dispensing a new dose each time. On January 5, 1960, the skin appeared normal, and the culture was negative.

This report should be closed by the statement that infections which arise at operation are evident at the first dressing. These will respond satisfactorily to this treatment or to exposure of the ear to the SO_2 gas in a chamber which will cover the ear. It is anticipated that either method will clean up resistant infections in those cases in which tympanoplasties are planned.

THE DE ROALDES AWARD.

At the recent annual meeting of the American Laryngological Association, the DeRoaldes Award and gold medal were presented to Dr. Dean M. Lierle as a great physician, surgeon, educator and humanitarian and in recognition of his services to otolaryngology and to the American Laryngological Association.

METHOD FOR THE IDENTIFICATION AND LOCALIZATION OF CEREBROSPINAL FLUID, RHINORRHEA AND OTORRHEA.*†

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(By Invitation),
and
G. O. PROUD, M.D.,
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This paper describes the experimental background as well as the practicality of a new method that can be used for the identification and localization of cerebrospinal fluid fistulae into the different cavities located within the base of the skull.

Several authors who studied the late complications of head trauma found that about one per cent of the patients presented this particular condition. Although injury is by far the main causative factor, ear, nasal and cranial surgery, infections, hydrocephalus and tumor can also bring about this problem. Surgery is frequently indicated to effect permanent cessation of the leakage, but the neurosurgeon is often hard put to determine the site of surgical attack. The otolaryngologist has been of modest help to the neurosurgeon in his difficulty.

The identification and localization of CSF leakage has depended almost entirely upon the clinical history and radiological findings. Various chemical tests have been advocated for the differentiation between spinal fluid and other secretions, but these sources of information are often insufficient and sometimes equivocal. The medical literature contains many reports attesting to this fact. For example, Lewin[1] reported about a patient with vasomotor rhinitis who was

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†From the Department of Otorhinolaryngology of the University of Kansas School of Medicine.

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submitted to craniotomy because of the incorrect diagnosis of CSF rhinorrhea. Ridley[2] in 1930 demonstrated that the lacrimal secretions contain as much reducing substances as the spinal fluid; therefore, the presence of this substance in any nasal secretion is inconclusive.

Concerning the localization of the site of leakage, Dandy[3] wrote: "Drainage of fluid from one nostril is fair evidence that the fistula is on the corresponding side of the anterior fossa, but that is by no means dependable proof. There are times when only an exploratory operation will determine the site of the opening, and there may be bilateral fistulae." He also stated that[3] "Drainage of CSF from the nose is not pathognomonic of a fistula into the frontal or ethmoid sinus, but may occur through the mastoid bone into the middle ear and Eustachian tube."

Roentgenological studies are of some aid in the localization of the general area of leakage, but as was pointed out separately by Morley and Hetherington,[4] Ecker,[5] Adson and Vihlein,[6] they are of little assistance in pointing out the exact site and of no assistance in the localization of CSF fistulae involving the ethmoid and sphenoidal sinuses.

Noting these problems several authors have tried different methods in an attempt to make the site of leakage objective. Fox[7] injected indigo carmine dye into the cisterna magna, but due to the poor contrast obtained, the usefulness of the method was limited to instances in which the rhinorrhea was copious. Crow and Keogh[8] injected radioactive sodium (Na^{24}) into the cisterna in two cases. Cotton pledgets were conveniently distributed in the walls and roof of the nose and nasopharynx and upon the openings of the frontal sinuses and Eustachian tubes. After their removal the pledgets were examined under a Geiger Mueller counter and the site of leakage was determined by the one showing the highest radioactive count. This technique, however, required specialized instruments for its performance and was an indirect method.

MATERIALS AND TECHNIQUE.

While doing studies on the inner ear with photoluminescent

substances the possibility of using fluorescein to detect the site of spinal fluid leakage became apparent. The advantages of this substance lie in its physical chemical and pharmacological properties. For example, the substance is photoluminescent; and under ultraviolet light its yellowish green glare makes it easily detectable from the surrounding environment. This is true even when it is mixed with other colored material such as hemoglobin, thus it is superior to formerly used dyes. The amount required for its detection is minimal

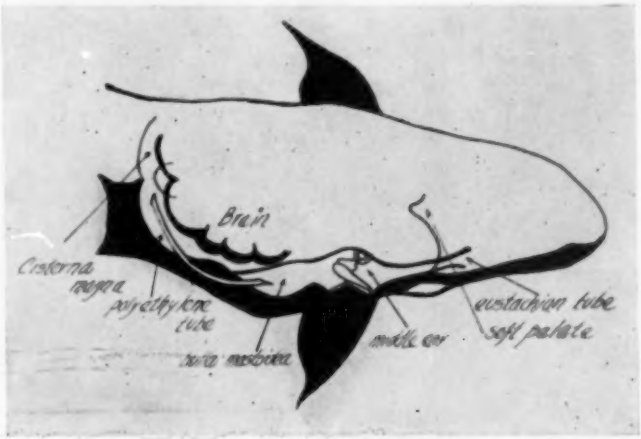

Fig. 1. Method of creating a cerebrospinal fluid fistula between the cisterna magna and bulla mastoidea in the experimental dog.

(1-1,600,000 dil.), and fluorescein's minute molecular structure makes for its ready diffusion in other fluids. Its chemical structure is stable and its mild alkalinity is not incompatible with body fluids. It is excreted by becoming bound temporarily to some of the plasma proteins. Its toxic effects are nil; Strauss[9] administered it orally in doses as large as 6 gms. with no outward effects, and Lange[10] recommended intravenous injection of 5 cc. of 5 per cent solution for determination of circulation time.

The dog was elected as the experimental animal, for its

anatomy was familiar and the available facilities for its care were superior. In three animals anesthetized by sodium nembutal, a fistula was created by inserting one end of a No. 18 polyethylene tube into the cisterna magna and the other as shown in Fig. 1, into the bulla mastoidea. This allowed the spinal fluid to flow into the respective Eustachian tube. Antibiotic therapy was administered for one week of convalescence. Direct visualization of the nasopharynx then revealed no evidence of fluid as shown in Fig. 2, but when

Fig. 2. Anesthetized dog.

1 cc. of 5 per cent fluorescein was injected into the spinal canal and the re-examination done under ultraviolet light the leakage was apparent in all three animals. Fig. 3 demonstrates fluorescein coming through left Eustachian tube.

In a fourth dog, under general anesthesia, after opening the bulla mastoidea a perforating burr was used to create a fistula between the middle ear cavity and the cranial fossa via the tegmen tympany. Fig. 4 shows the place of the fistula (marked by an arrow) just above the round window. One cc. of fluorescein was injected into the spinal canal in the

lumbar area and ultraviolet examination disclosed, as shown by Fig. 5, the fluorescent materials both on observation through the bullar opening as well as through the tympanic membrane.

The final steps of the experiment were performed upon the human on demand by the Department of Neurosurgery which had heard of the animal experiments.

Fig. 3. Anesthetized dog under ultraviolet light showing the glare of fluorescein in the opening of the left Eustachian tube.

To meet these clinical problems a technique of examination was developed. The initial step was the cocanization of the nose and nasopharynx followed by the insertion of a cotton pack midway in the nasal chambers (see Fig. 6). Divided in this way it was possible to detect where the leakage was located. For example, fluorescein detected under the middle turbinate anterior to the pack was necessarily coming from the frontal sinuses (see Fig. 7). If the fistula was located in the cribiform plate the fluorescein was detected upon the midline in the nasal septum (see Fig. 8); leakages coming through the sphenoidal sinus could have been easily discovered

Fig. 4. Photograph of middle ear; note the round window and arrow showing the site where the fistula was created (10X).

Fig. 5. Photograph of middle ear of the dog, under ultraviolet light; arrow pointing to the glare of fluorescein leaking through the created fistula (10X).

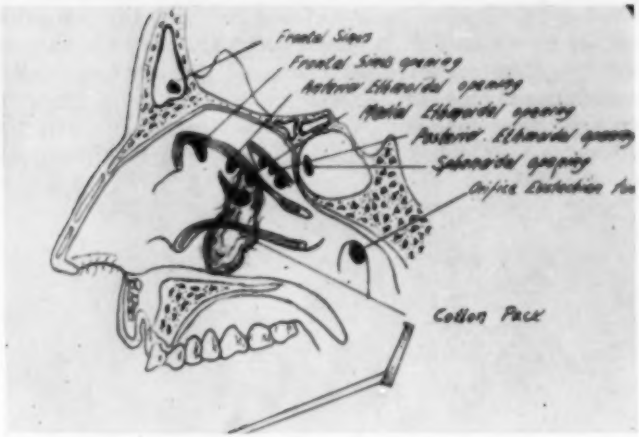

Fig. 6. Location of cotton pack in the nose.

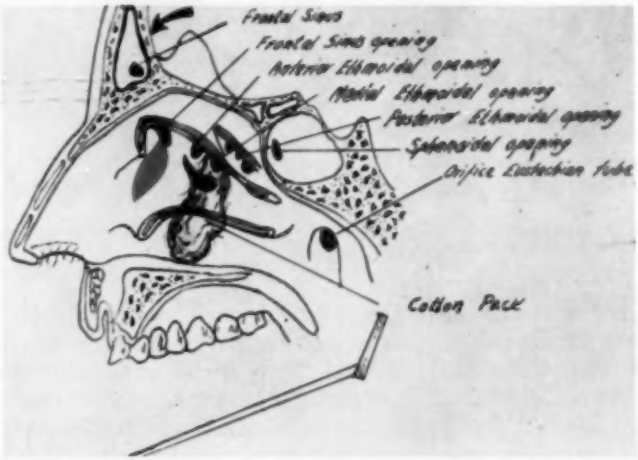

Fig. 7. Leakages through the frontal sinus can easily be discovered in the opening of the nasofrontal duct in the nose.

by indirect nasopharyngoscopy under ultraviolet light. Fistulas from the middle cerebral fossa involving the petro-tubal area, as shown in Fig. 9, would cause fluorescence upon the respective Eustachian tube openings. In cases of leakage through the middle ear or tegmen mastoidea the fluorescence would become apparent in the respective Eustachian tube opening as well as behind the respective tympanic membrane (see Fig. 10).

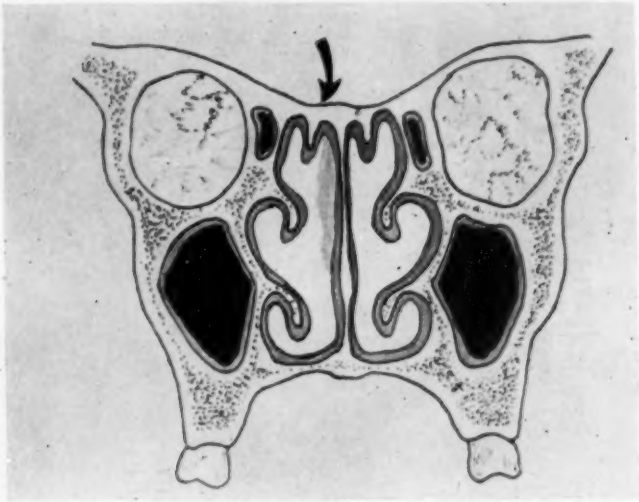

Fig. 8. Leakages through the cribiform plate can be discovered on either side of the nasal septum.

The first case investigated by this method was that of an adult female complaining of hearing loss in the right ear following an automobile accident. X-ray studies of the skull were negative. Examination revealed a hemotympanum. One cc. of 5 per cent fluorescein was injected into the lumbar spine, and the patient was placed in a prone position with the head slightly dependent for 15 minutes. Ultraviolet examination of the ears was then carried out and fluorescence was observed in the escaping fluid following myringotomy. The

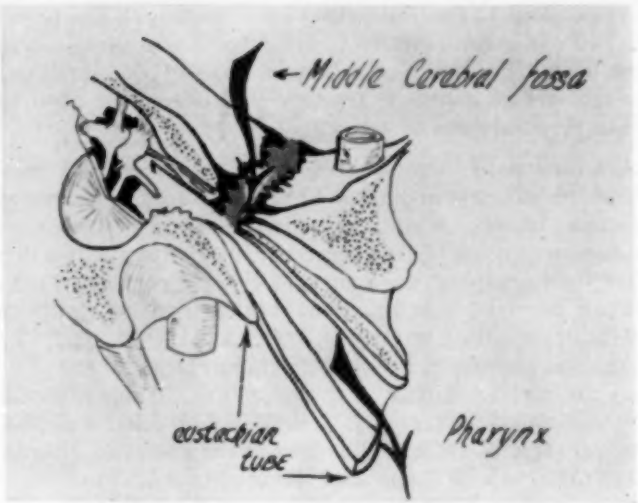

Fig. 9. Fistula involving the petro-tubal area.

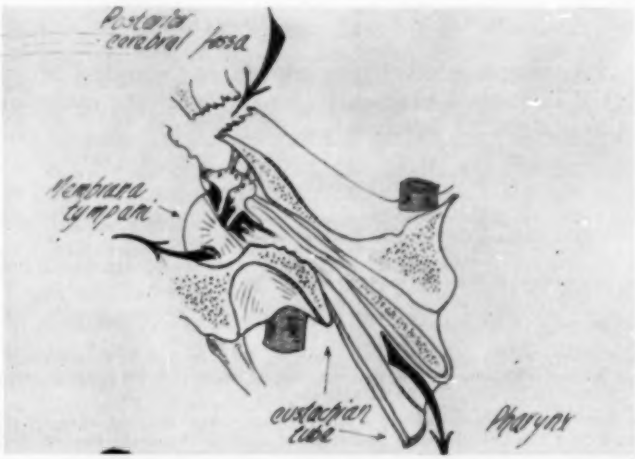

Fig. 10. Fistula of the tegmen mastoidea; fluorescein present at the Eustachian tube opening and tympanic membrane.

same material was discovered in the nasopharynx in the area corresponding to the Eustachian tube opening. The patient did well under conservative treatment. It was three months later, and after two X-ray examinations of the skull were performed that a line of fracture was discovered upon the middle cerebral fossa.

A second patient, a 24-year-old male was involved in an automobile accident at the age of 18. He had experienced six attacks of meningitis and had undergone surgery seven times for closure of dural tear evidenced by intermittent rhinorrhea. After the intraspinal injection of 1 cc. of 5 per cent fluorescein an ultraviolet examination was carried out with the patient in the sitting up position and in a darkened room. The fluorescent material was found coming anterior to the previously inserted nasal pack near the midline. The assumption was that the fracture was located in the cribiform plate. Surgical exploration found the tear at the predicted site, and it was repaired with fascia lata. Four months later meningitis recurred and an identical leak was found by the same method though rhinorrhea was not apparent without fluorescein study. Surgical repair was again performed, this time with success.

CONCLUSIONS.

1. Fluorescein injected intraspinally and searched for under UV light is of practical value in the identification and localization of CSF leakages.

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VIIeme INTERNATIONAL CONGRESS OF OTOLOGY, RHINOLOGY AND LARYNGOLOGY.

The Seventh International Congress of Otology, Rhinology and Laryngology will be held in Paris, July 23-29, 1961, at the New Faculte of Medicine, Rue des Saints-Peres. The program includes *1.* The Recent Acquisitions, Pathology and Therapeutics of Otosclerosis by Profs. Sourdille, Sercer and Krmpotic, Weber, Ardouin, Larroude, Ferreri and Shambaugh. *2.* Indications and Five-Year Results in Surgery and Radium in the Treatment of Cancers of the Larynx and Hypopharynx—Profs. Pietrantoni and Agazzi Alonzo, Casadesus, C. L. Jackson, Leicher, Leronx-Robert and Ormerod. *3.* A Report on Allergy and Infections of the Nose and Bronchus—Profs. Van Dishoeck, Clerici, Hlavacek, Voohorst, Mayer, Laskiewicz and Terracol.

Tours and entertainment for guests and their ladies have been arranged. President: Dr. Maurice Aubry; Secretary General: Henry Guillon. For further details write Dr. Guillon, 6 Avenue McMahon, Paris, France.

ISOLATED LARYNGEAL KERATOSIS.

Its Relation to Carcinoma of the Larynx Based on a Clinicopathologic Study of 87 Consecutive Cases With Long-Term Follow-Up.*†‡

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INTRODUCTION.

The relationship of keratosis of the larynx (variously termed hyperkeratosis, leukoplakia and pachydermia laryngis), to cancer, has been the subject of a number of case studies.[1-9] All generally support the view that metaplasia and keratinization of the laryngeal mucosa are associated with the subsequent appearance of invasive epidermoid carcinoma. The implication is that isolated keratosis can unexpectedly and unpredictably undergo "transformation" or "metamorphosis" to cancer.[1,4,6,10,15] The concept of the "malignant potential" of laryngeal keratosis has become so widely accepted that few individuals have asked critical questions or have been skeptical of the prevalent view.[16,17]

With the recent interest in cancer prevention by treating "precancerous" lesions, the conservative therapy of the past for the management of keratosis is yielding to change. Some laryngologists now advocate treating this lesion in remark-

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ably radical ways, *e.g.*, laryngofissure,[8,15] laryngectomy[13,18] and irradiation with cancerocidal doses[13,15,16]—ways usually reserved for treatment of cancer itself. The preoccupation with a chance for successful cancer prevention and cure has tended to hide the hard fact that the magnitude of the risk of cancer in keratosis patients is unknown as yet and that therapeutic procedures for cancer of the larynx are known to be associated with appreciable risks of morbidity and laryngeal dysfunc-

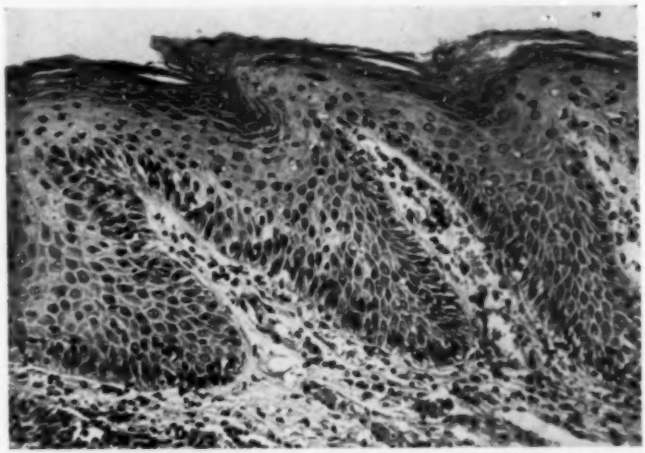

Fig. 1. This area shows hyperkeratosis with minimal epithelial hyperplasia. There is acanthosis and a regular maturation of the spinous layer to form a well-developed granular layer. A thin layer of acellular keratin is formed on the surface. No atypia is seen. This is classified as HK. Case 1. W.U. Ill. 59-6936A. (X275.)

tion.[19,20,21] Before permitting keratosis patients to undertake such risks, either of developing cancer or of morbidity and laryngeal dysfunction from cancer prophylaxis, it is imperative that the relationship between keratosis and cancer be more closely investigated.

It would seem, therefore, that a careful clinical and pathological analysis of a group of patients with isolated laryngeal keratosis correlated with the results of long term follow-up

might clarify the situation and supply prognostically significant information. The work of Putney and O'Keefe[18] represents the only other study with a somewhat similar approach to the problem. Their conclusions, which support the concept of the precancerous nature of keratosis, are at variance with the results of this study and will be discussed.

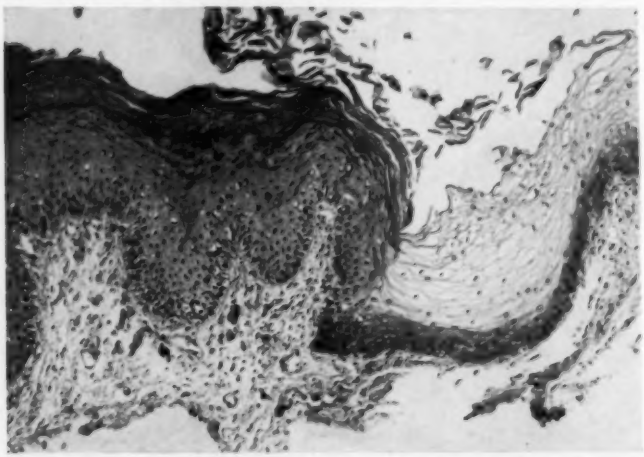

Fig. 2. Note the epithelial alterations of hyperkeratosis on the left with orderly maturation and granular layer formation topped by a thick layer of acellular keratin in continuity with an area of parakeratosis showing surface accumulation of keratinized cells with retention of nuclei. No atypia is present. For classification purposes this is HK. Case 2. W.U. Ill. 59-3518A. (X150.)

MATERIAL AND METHODS.

All of the laryngoscopic biopsies accumulated during the years 1945 through 1954 were reviewed by two of us independently and without knowledge of the clinical findings or subsequent course. The histologic alterations were classified (see below). On the basis of these studies and analysis of the histories, clinical findings and diagnoses all cases of squamous carcinoma, squamous papillomas, laryngeal vocal nodules, contact granulomas and nonspecific inflammatory lesions associated with minimal epithelial alterations were

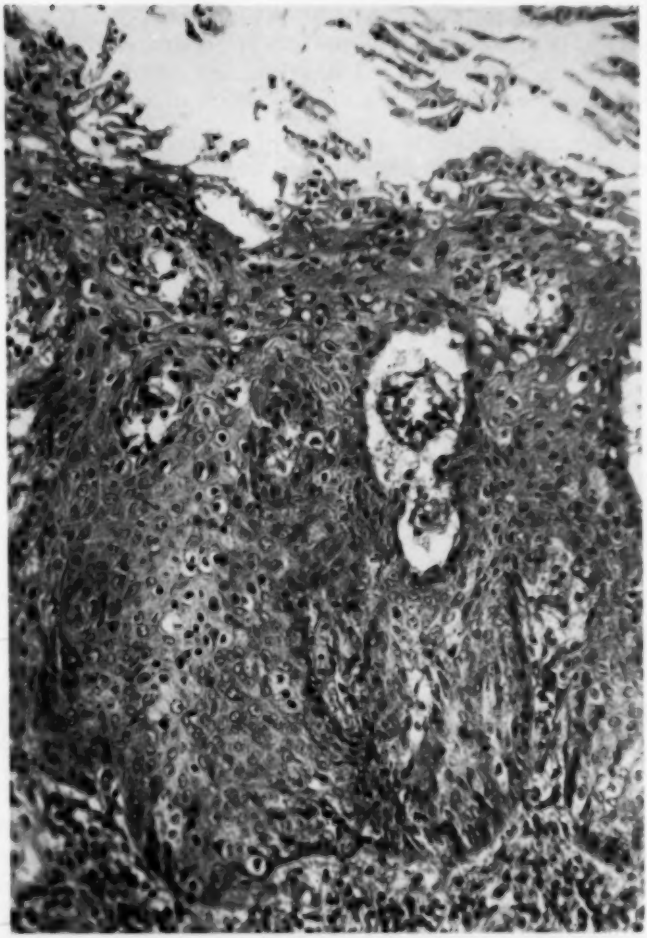

Fig. 3. A parakeratotic area from a subsequent biopsy showing disturbed maturation in deeply acanthotic epithelial folds. The nuclei present considerable variation in form and chromatin distribution. This is classified as PKA. Case 2. W.U. Ill. 59-3519A. (X250.)

excluded. There remained 87 consecutive cases of isolated laryngeal keratosis. All of these patients have been followed to date, December, 1959, or to death, a minimum of five and a maximum of 15 years, and all subsequent pathological specimens have been studied and clinical observations recorded.

The normal epithelial covering of the larynx is nonkeratinized squamous epithelium, except for the laryngeal ventricle

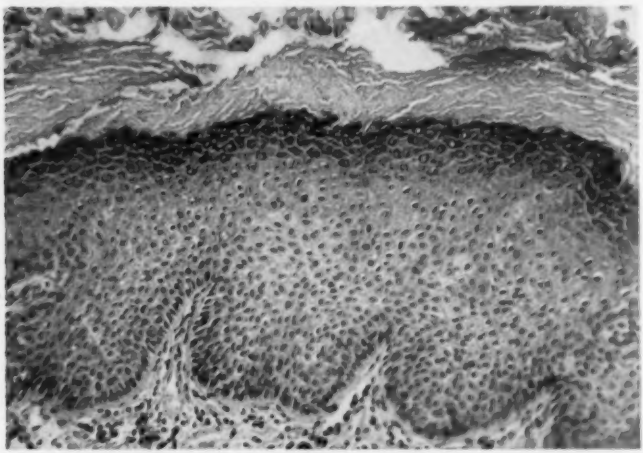

Fig. 4. A typical area of hyperkeratosis showing a thick hyperplastic epithelium with a uniform and orderly maturation of cells to form a thick keratohyalin granular layer. A layer of desquamating keratin tops the lesion. Typical HK. Case 4. W.U. Ill. 59-3516A. (X250.)

and subglottic area where pseudostratified, ciliated, columnar epithelium exists. *Epithelial hyperplasia,* defined as thickening with or without acanthosis; *parakeratosis,* defined as the surface accumulation of incompletely keratinized cells retaining their nuclei; *keratosis* and *hyperkeratosis,* defined as the formation of a granular layer with surface accumulation of completely keratinized cells; *epithelial atypia,* defined as abnormal maturation of the epithelial cells with nuclear abberation, but of insufficient degree to be classified as carcinoma-*in situ,* are the morphologic alterations that were studied. On

this basis each case was placed in one of four groups: hyperkeratosis, HK; parakeratosis, PK; hyperkeratosis with atypia, HKA; parakeratosis with atypia, PKA (see Figs. 1, 2, 3, 4, 5 and 7).

RESULTS.

On subsequent biopsy, at intervals of 2.5, one and one

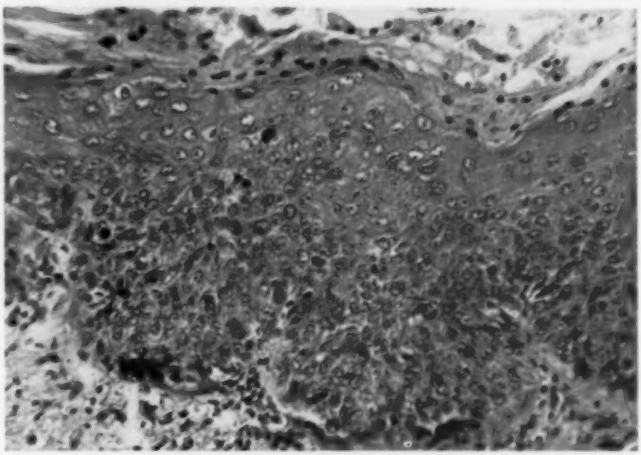

Fig. 5. Another area in the same biopsy showing disorderly maturation of cells most apparent in the deeper zones but present to a degree even in the top zone. Such areas, as depicted here, often fail to completely keratinize and are parakeratotic. This is PKA. Case 4. W.U. Ill. 59-3517A. (X310.)

months respectively, three of these 87 cases were found to have squamous carcinoma. These cases are not interpreted as "quick metamorphosis" of keratosis into carcinoma as suggested by Priest,[9] but simply as the association of keratotic changes and invasive cancer—a very frequent finding[22]—in which the first biopsy was taken from an unrepresentative area. This is a remarkably low incidence for this course of events and speaks highly of the accuracy of the laryngologists' biopsy samples and the thoroughness of the pathological examination, for 470 cases of carcinoma of the larynx were

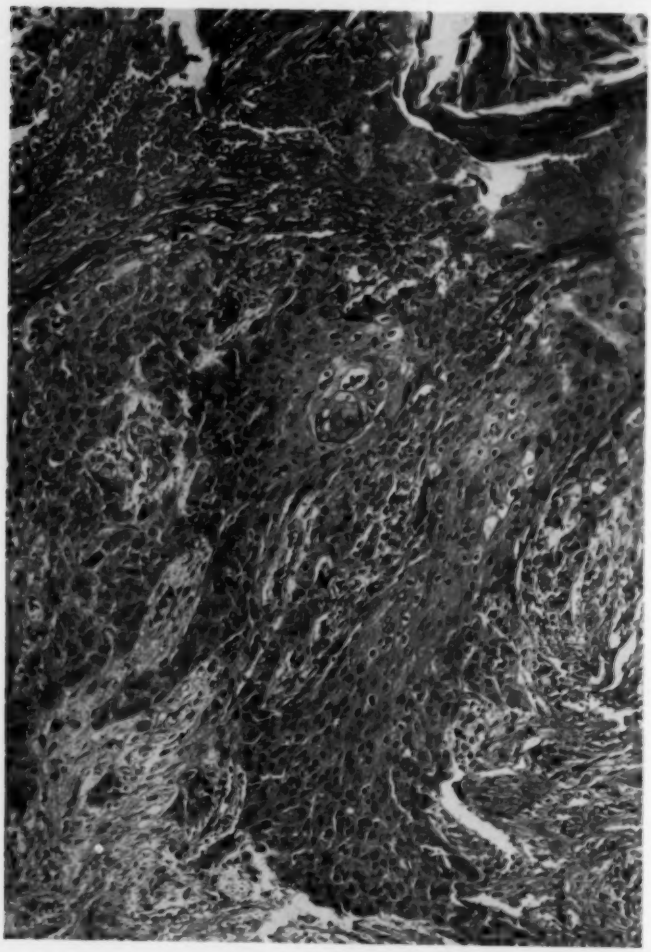

Fig. 6. Same case as Figs. 4 and 5. This biopsy, taken six years later, shows an invasive epidermoid carcinoma. W.U. Ill. 59-3515A. (X130.)

diagnosed by biopsy during this same period. An incidence of 0.2 per cent for this "error" lays to rest, we hope, the debate concerning the accuracy of biopsy and/or histologic examination. These three cases, all in males, are considered squamous carcinoma from the onset.

Of the 84 remaining cases, 74 were male and ten female. The mean age for the males is 51.7 years and for the females

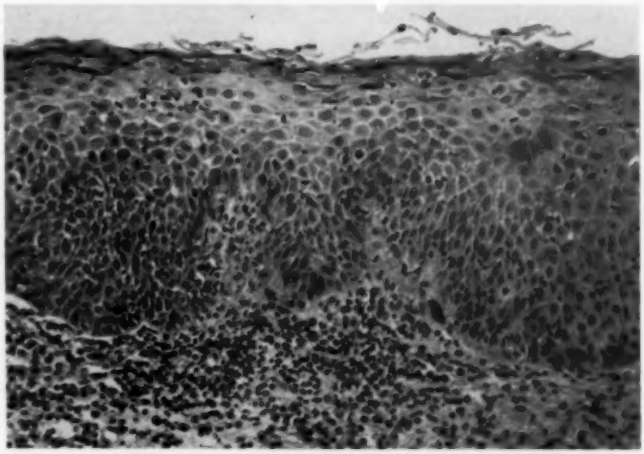

Fig. 7. An area from a biopsy taken in 1951 showing epithelial hyperplasia, atypia and parakeratosis. Other areas were interpreted as HKA. Case 5. W.U. Ill. 59-3523A. (X275.)

50.5 years. The distribution of cases by decades of age is shown in Table I. The dominant symptom was hoarseness, which was present for varying lengths of time as shown in Table II. The areas of the larynx involved by keratosis are shown in Table III. No correlation is found between site of involvement and duration of symptoms or histologic changes. The nine cases with involvement of the interarytenoid area and the posterior portions of both vocal cords correspond to what has been called pachydermia laryngis.[4] None of these nine cases developed invasive carcinoma.

TABLE I.

Distribution by Decades of 84 Patients with Laryngeal Keratosis.

	Decades					
	20-29	30-39	40-49	50-59	60-69	70-79
Males	2	10	20	18	20	4
Females	0	3	2	3	1	1
Total	2	13	22	21	21	5

TABLE II.

Duration of Hoarseness Prior to Biopsy in 84 Patients with Laryngeal Keratosis.

	Months						
	0-6	7-12	13-18	19-24	25-30	30+	Unknown
Number of Patients	44	7	8	0	6	17	2

TABLE III.

Sites of Laryngeal Involvement by Keratosis, 84 Patients.

	Number of Cases	Per Cent
Both True Vocal Cords	28	33
Left True Vocal Cord	16	19
Right True Vocal Cord	13	15
Both Vocal Cords and Interarytenoid Area	9	11
Interarytenoid Area Only	8	10
Miscellaneous	10	12
	84	100

TABLE IV.

Histologic Classification, Mean Ages, Years Followed. 84 Cases of Laryngeal Keratosis.

Histologic Subgroup*	No. of Cases	Mean Age, Years	Mean Years Followed
HK	35	51.8	7.0
PK	31	47.3	8.0
HKA	13	61.5	7.2
PKA	5	52.0	6.4

*See text for definition of these groups.

We have no conclusive evidence regarding inciting agents or causal factors. Symptomatically a few individuals improved after the cessation of excessive smoking or the institution of voice therapy, but the significance of this is uncertain.

The histologic classification of the keratotic lesions in these patients is found in Table IV. Included are the mean age of

the patients in each sub-group and the average number of years the patients were followed. As previously mentioned all of these patients have been followed to date or death. Those alive have been questioned as to persistence of symptoms, further therapy and, where possible, current laryngoscopic observations recorded. The cause of death is known in all patients dead.

The number of cases with recurrence or persistence of hyperkeratosis is estimated in two ways (see Table V): one,

TABLE V.

Recurrence of Hyperkeratosis in 84 Cases as Determined by (a) Multiple Biopsies and (b) Peristence of Symptoms (Hoarseness).

Histologic Subgroup*	(a) Multiple Biopsies	(b) Symptomatic	(b) Asymptomatic	(b) Unknown
HK	10	12	20	3
PK	4	13	13	5
HKA	10	10	1	2
PKA	1	1	4	0
Total	25	36	38	10

*See text for definition of these groups.

those cases proven by subsequent biopsies and two, those cases with persistent or recurrent hoarseness. Twenty-five of the 84 cases (30 per cent) had recurrence proven by biopsy. Close to half of the cases had persistence of hoarseness and presumably of hyperkeratosis. The true recurrence or persistence rate lies somewhere between the two estimates. A high percentage (73 per cent) of patients with epithelial atypia in addition to keratosis had persistence of symptoms and multiple biopsies. Table IV shows the distribution of the lesions in the 25 cases with multiple biopsies.

Laryngeal keratosis may occasionally involve large areas, appear quite aggressive and narrow the glottis enough to necessitate tracheotomy for respiratory distress; two such cases were found. Unless the repeated endoscopic excisions in such cases are done with care a useless larynx may result. Two instructive cases in this series with extensive and refractory lesions are reported herein.

Case 1. G.B., a 60-year-old white insulation service manager, was first seen in December, 1946, having been intermittently hoarse for ten years. He abused his voice, shouting at work, and subsequently was found to have a positive serologic test for syphilis. Endoscopic examination showed thickened red-gray vocal bands with involvement of the left aryepiglottic fold. Biopsies were taken that showed hyperkeratosis. Over the ensuing 12 years he was admitted to the hospital 44 times and 46 biopsies and strippings of both true and false cords and extensive areas of the supraglottic mucosa performed. All of these showed hyperkeratosis, epithelial hyperplasia and occasionally slight epithelial atypia. The last biopsy was taken in December, 1957. Carcinoma was never found. His voice improved somewhat after each excision, and though he decreased smoking he did not stop. He died in May, 1958, of heart failure without evidence of laryngeal cancer. Due to the care taken by his laryngologist his larynx remained functional, though his voice was hoarse (see Fig. 1).

TABLE VI.

Distribution of Recurrent Isolated Keratosis in 25 Cases with Multiple Biopsies.

Site	No. of Cases	Proposed Therapy*
One Cord	5	Laryngofissure
Both Cords	11	Irradiation Therapy
Entire Larynx	3	Laryngectomy
Both Cords and Subglottic Area	1	Laryngectomy
"Pachydermia Laryngis"	3	
One Cord and Interarytenoid Area	1	Conservative Measures
Interarytenoid Area Only	1	Conservative Measures

*See text.

Case 2. I.L., a 73-year-old white male merchant, was seen in June, 1948, with a history of hoarseness for two years and a white plaque on the anterior third of both cords with involvement of the anterior commissure. The first and eight subsequent biopsies, over the ensuing nine years, showed extreme hyperkeratosis with moderate atypia. Each stripping was associated with marked improvement in the quality of his voice. He was last seen in March, 1959, at the age of 84, with a small quiescent white patch on the left cord. Keratotic involvement in this case has been limited to the true cords and anterior commissure. Carcinoma has not presented itself, and this man still has a functional larynx (see Figs. 2 and 3).

The results of the follow-up study on the 84 determinate cases are shown in Table VII. Three of these 84 patients developed carcinoma of the larynx: one, nine months; one, six years, and the other eight years after the initial biopsy demonstrating keratosis.

Case 3. M.K., a 50-year-old policeman was seen in January, 1954, complaining of intermittent hoarseness of one year's duration and a 30-pound weight loss. Laryngoscopy showed a rough white lesion involving both true cords. Biopsy showed hyperkeratosis. Nine months later the patient was seen at another hospital by another physician for persistent symp-

tomas. Another biopsy showed invasive epidermoid carcinoma, and he was treated by irradiation therapy. Persistent cancer was found three months later and a laryngectomy demonstrated a 4x3 cm. poorly differentiated carcinoma with blood vessel invasion. Tumor was present at the surgical margins. Stomal recurrence was noted a few months later and he died 19 months after his first biopsy.

Case 4. H.J., a 64-year-old negro laborer, was first seen in September, 1952, complaining of painless hoarseness of one year's duration. Laryngoscopic examination showed leukoplakia of the anterior third of the left vocal cord without change in its mobility. A biopsy and stripping demonstrated hyperkeratosis and atypia (see Figs. 4 and 5). He was not seen again until August, 1955, when he returned complaining of hoarseness. A small white plaque on the anterior third of the right cord was biopsied, but no histological abnormalities were seen. In September, 1958, he was admitted to St. Louis Veterans Hospital, a lesion of the left vocal cord was biopsied, diagnosed as squamous carcinoma and a laryngectomy done (see Fig. 6). He is alive without evidence of metastases to date.

TABLE VII.

Survival of Patients with Isolated Keratosis Followed for Five to 15 Years (1945-1955).

87 Cases—Total Series.	
3 Cases—"Missed Carcinoma."*	
84 Cases—Determinate Series.	
Three Cases Developed Invasive Epidermoid Carcinoma—	
1 case 9 months post biopsy; died of cancer 10 months later.	
1 case 6 years post biopsy; alive and well.	
1 case 8 years post biopsy; alive and well.	
81 Cases Did Not Develop Epidermoid Carcinoma—	
55 cases alive and well.	
26 cases died of unrelated disease.	
12 cardiovascular.	
7 cancer.	
2 each lung and liver.	
1 each breast, stomach and soft tissue (sarcoma).	
7 miscellaneous (cirrhosis, tuberculosis, asthma, etc.).	

*See text.

Case 5. S.W., a 57-year-old white male, was first seen in May, 1951, having been hoarse for six to eight years. Laryngoscopic examination showed thickening, keratosis of the posterior third of each cord, more marked on the left. Biopsies done in May and December of 1951 and November of 1953 showed epithelial hyperplasia, minimal hyperkeratosis and moderate atypia (see Fig. 7). No therapy was given. In April, 1959, he was seen with an exophytic mass on the posterior half of the left vocal cord. This was biopsied and diagnosed as invasive squamous carcinoma (see Fig. 8). He received irradiation therapy and has a functional larynx to date.

Case 3 is different from Cases 4 and 5. Although the development of carcinoma is beyond the three-month time limit for cases designated as a "missed carcinoma" its size, extent

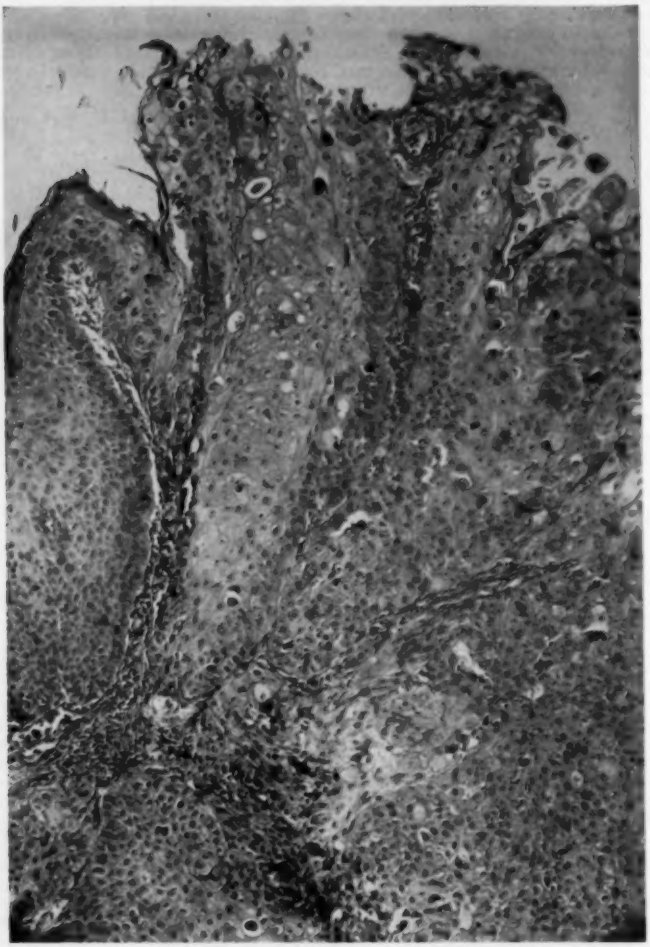

Fig. 8. Same case as Fig. 7. This invasive, well differentiated keratinizing carcinoma was found on biopsy eight years later. W.U. Ill. 59-3521A. (X115.)

and rapid evolution to death in spite of therapy are in favor of its having been cancer from the onset. In addition, the size of the initial biopsies was not what we consider adequate at the present time for a laryngeal lesion of the extent initially described. This is the only case of this nature in this series and emphasizes the need for adequate sampling; however, we prefer to classify this case as one of carcinoma developing in a larynx with hyperkeratosis.

Cases 4 and 5, both in the HKA histologic group, may be considered in three possible ways. The first is that they also represent carcinoma present from the onset but overlooked for a period of six to eight years. This is most unlikely in view of the repeated examinations and biopsies and the natural history of laryngeal cancer. A second possibility is that the sequential appearance of these lesions is purely coincidental. Finally, there is the possibility that isolated keratosis is truly precancerous and that in some way as yet unknown, carcinoma arises from the keratotic lesion. In order to support this last possibility it would be necessary to demonstrate that the number of cases of carcinoma of the larynx encountered in a group of patients with laryngeal keratosis represents a significantly increased incidence when compared to a suitable control group.

Attempts to analyze our data statistically yielded no conclusive information in that we were unable to prove that the patients with keratosis, as a group, had the same laryngeal cancer incidence as the general population. Nor could we prove that the incidences differed significantly.

The analysis failed because the minimum requisite statistical data were not available: *i.e.*, we do not know the true incidence of keratosis in the general population or at autopsy; and we have too few cases of keratosis followed by cancer. The statistical relationship between keratosis and carcinoma of the larynx will not be known until considerably larger numbers of patients with keratosis are studied with long-term follow-up and until accurate data related to the incidence of laryngeal carcinoma in a suitable control population become available.

DISCUSSION AND COMMENT.

The recent attention given to the treatment of premalignant lesions and early cancer by ablative surgery or irradiation therapy[6,13,15,18] as well as the popular notion of the precancerous nature of laryngeal keratosis[1,4,6,10-15] should at least be supported by the demonstration of an appreciable risk of malignancy attendant upon conservative management; further, it should be shown that the risk of mortality, morbidity and loss of function attending any proposed therapy be less than the risk of associated or subsequent malignancy. Ultimately it would be desirable if some rational cause and effect relationship could be established between the proposed "premalignant state" and invasive cancer. In our present state of ignorance regarding the pathogenesis of cancer this last requirement, at least for keratosis and epidermoid carcinoma of the larynx, is impossible to establish. The influence of occupational irritants, chronic laryngeal inflammation, voice abuse, smoking, alcohol intake, vitamin deficiencies and structural laryngeal abnormalities, all factors considered of importance in relation to keratosis provide, as yet, no rational causal explanation for the development of carcinoma.

In our opinion the premalignant nature of keratosis and the metamorphosis of keratosis to cancer are based in the main upon repetition of previously reported case material with an increment each time of a few more clinical cases. These studies certainly raise the question of a premalignant state, but they hardly serve to provide the requisite clinical proof.

In the absence of statistical evidence of the malignant potential of laryngeal keratosis, clinical judgment must rest upon the results of series of consecutive cases treated conservatively. The observations of Putney and O'Keefe[18] on 68 cases of keratosis are most pertinent. Of their 68 patients, 27 later developed carcinoma. Of these 27, six were found within six months. They consider these six cases as carcinoma from the start and these cases are comparable to the three in our group in which cancer was evident within 2.5 months. Having excluded these six, 62 cases treated con-

servatively remained and of these 21 developed carcinoma over a period ranging up to ten years, ten within two years and 11 thereafter.

The ratio of cases eventually developing cancer to total cases (21 of 62) in the Putney and O'Keefe series does not compare favorably with the results of the present series (three of 84). We have not found any important differences between these two groups of patients with keratosis to explain this difference. The age range, mean age, sex ratio and mean duration of laryngeal symptoms are approximately the same. Perhaps some unknown patient selection factors and differing pathologic criteria are responsible for the observed variance.

In our experience conservative therapy has yielded most gratifying results. With careful cooperation between the laryngologist and pathologist the risk of missing cancer in any of its stages is very small. Our evaluation of these results is that the risk of subsequent carcinoma in carefully followed patients with keratosis is so small as to obviate the necessity of prophylactic anticancer treatment. This evaluation finds additional support from the following considerations. Suppose the most advanced and recent thinking on the therapy of keratosis[15] were utilized in our series of cases. This would call for laryngofissure for recurrent keratosis limited to one vocal cord, irradiation therapy for recurrences involving both vocal cords and laryngectomy for irradiation failure and recurrences with extensive papillomatous involvement of the larynx. Pachydermia laryngis and posterior commissure lesions would be treated conservatively. Of the 25 cases in our series with proven recurrent keratosis (see Table VI), five would have had laryngofissure; 11, irradiation therapy and four would be considered candidates for laryngectomy. We are unable to say that this treatment plan would have prevented a single case of laryngeal cancer. None of the cases that would have had surgical therapy subsequently developed carcinoma and ten of the 11 candidates for X-ray therapy are also free of cancer. One case (Case 5) might have benefited from X-ray therapy in that his recurrent keratosis might have disappeared; however, irradiation therapy

does not help all such cases[12,13,18] and there is no evidence that such therapy actually prevents the subsequent appearance of malignancy. These views are made even more compelling when one realizes that the X-ray therapy actually given for the true cord carcinoma that appeared in this case (Case 5) would have been an impossible therapeutic consideration had prior irradiation been given for keratosis; and the surgical risk of morbidity in operating in an irradiated field is also increased. Finally, emphasis should be directed to the fact that the proposed therapy would not have prevented two of three cases of carcinoma (Cases 3 and 4) in this series because these two patients did not have a recurrence of keratosis after nine months and eight years respectively, but rather the reappearance of hoarseness heralded the presence of invasive carcinoma.

Conservative therapy, in the form of investigation and exclusion of irritant factors known to be associated with keratosis, adequate laryngeal examination at properly timed intervals together with careful biopsy and stripping of the involved mucosa, has proven adequate in all cases. The appearance of cancer in patients of this series with atypical epithelial alterations is some indication that these patients should be followed with greater care.

Several well defined lesions and some less well categorized conditions are associated with hyperplasia and keratinization of the larynx, particularly the vocal cords. Of these chronic hypertrophic laryngitis, squamous papillomas, laryngeal vocal nodules and squamous carcinoma are more frequent than isolated keratosis. The gross differentiation of these lesions is not difficult for the experienced laryngologist, and the microscopical appearance is characteristic. The exception is the gross differentiation of isolated keratosis from well differentiated keratinizing squamous carcinoma. Here the laryngologist must rely on the pathologist's interpretation of the biopsy and the pathologist must accept the responsibility of his diagnosis. Equivocal diagnoses, such as "almost a keratinizing squamous cell carcinoma," "epithelial papillosis, perhaps malignant" and "very like cancer,"[13] are of no help to the laryngologist. They serve only to create a climate of

confusion in which every pathologic diagnosis of keratosis is viewed with suspicion and apprehension. Even worse, they may force him to the use of radical therapeutic procedures for a manifestly benign condition. When close cooperation exists between a laryngologist who takes accurate biopsies and an experienced pathologist who makes a careful study of the material, the error in assessing the true nature of the laryngeal lesion is sufficiently small to place confidence in the use of conservative measures in the management of isolated keratosis.

SUMMARY.

Eighty-seven individuals with clinical and histological findings of laryngeal keratosis have been followed for a minimum of five and a maximum of 15 years. The age, sex, anatomical and pathological characteristics of the group are defined.

Three individuals were found on subsequent biopsy, within three months, to have invasive carcinoma. These are considered to have had carcinoma from the onset that was missed by the first biopsy. They represent an incidence of less than 0.5 per cent for this "error" among the 470 cases of laryngeal carcinoma diagnosed during the time under study.

Of the remaining 84 cases, three developed laryngeal carcinoma at intervals of nine months, six years and eight years respectively after the diagnosis of keratosis. One of these three patients died of laryngeal carcinoma. Two are alive and well without evidence of persistent disease: one following laryngectomy and one following irradiation therapy.

Eighty-one patients did not develop laryngeal carcinoma. Of these 55 are alive and well to date while 26 died of unrelated diseases. Of the 25 cases with biopsy proven persistence of keratosis and the 36 with symptomatic persistence, one developed laryngeal carcinoma.

These findings do not support the prevalent concept that laryngeal keratosis is a distinct precancerous condition. Analysis of the data does not support the institution of prophylactic anticancer therapy, *e.g.*, laryngofissure, irradiation and laryn-

gectomy for patients with laryngeal keratosis. The theoretical application of these measures to our series shows that not a single case of cancer would definitely have been prevented and emphasizes the risk of morbidity and laryngeal dysfunction attending such procedures.

Conservative therapeutic measures, careful follow-up laryngeal examinations with biopsy as indicated have proven adequate in the patients studied.

The morphologic alterations are classified, defined and illustrated. Individuals with atypia as well as keratosis have a higher incidence of persistence and should be observed more closely.

ACKNOWLEDGMENTS.

We thank the following physicians for their cooperation in this study: Dr. B. C. Adler, Dr. W. T. K. Bryan, Dr. A. J. Cone, Dr. J. B. Costen, Dr. H. M. Cutler, Dr. Morris Davidson, Dr. L. W. Dean, Dr. Guerdan Hardy, Dr. C. C. Jacobs, Dr. E. H. Lyman, Dr. A. W. Proetz, Dr. B. H. Senturia, Dr. A. C. Stutsman, Dr. R. E. Votaw, Dr. T. E. Walsh and Dr. J. W. West.

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THE JAMES E. NEWCOMB AWARD.

Dr. Joel J. Pressman, of Los Angeles, was chosen by the members of the American Laryngological Association at its annual meeting recently, to be the recipient of the James E. Newcomb Award for his outstanding contribution to research in otolaryngology.

SKIN GRAFTING IN PARTIAL AND COMPLETE LARYNGO-PHARYNGECTOMY AND CERVICAL-ESOPHAGECTOMY.*†

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When dealing with large advanced carcinomatous lesions of the laryngopharynx and adjacent cervical esophagus, one must assume the attitude of an optimist, for at best the five year survival rate is poor with either surgery, or irradiation. If one can count either as definitive, surgery would certainly be the choice. The extensive surgery that must be done is not without its complications and hazards. As to life of the patient, the ultimate poor results are not gratifying.

When the continuity of the pharynx and esophagus is interrupted in order to remove all the cancerous tissue, some type of reconstruction must be done in order to form a new gullet for the passage of food and saliva. Prior to the antibiotic days this was almost an impossibility, though Trotter[1] mentioned it with much enthusiasm in 1913. Esser,[2] in 1917, first described the principle of inlay grafting of split thickness skin supported by a solid mold or stent for mouth lesions. The use in the laryngopharynx had to await the advent of chemotherapy and antibiotics for its success. Wookey[3] established the really first successful method in his two stage procedure in 1948. By the use of skin flaps and reconstructive procedures he was able to form a new pharynx. This method was often fraught with complications, temporary pharyngostomes and sometimes weeks of hospitalization. In 1950 Owen and Negus[4] were the first to reconstruct the pharynx and cervical esophagus in a one-stage procedure by means of a free split thickness graft held in place by a stent

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or mold. Others have followed, using various materials as molds or stents to preserve the continuity of the pharynx with the esophagus until the graft was secure. Pressman,[5] experimentally in animals, has used the lyophilized aorta as a homograft to close this defect with very interesting results. Som[6] has used a portion of the upper trachea and larynx with partial skin grafting to close the defect produced by surgery when the pharynx and a portion of the cervical esophagus was removed. Any lesion involving the pharynx and requiring the removal of more than 70 per cent of its circumference is more than likely to end with a stricture or incomplete healing.

The original tube stent was first made by Negus,[7] of polyethylene tubing, and later the irregular shaped tube conforming more to the shape of the pharynx and laryngopharynx was made of latex rubber and used by Shaw and Ormerod[8] rather extensively. Conley[9,10] has used both the tantalum wire mesh, tubal plastic stent and also woven nylon stent in a number of cases reported with success. Much the same results have been obtained by others who have attempted to reconstruct the pharynx and cervical esophagus when either the complete circumference was removed or a sufficient amount so that primary closure was thought impossible.

Briefly before reviewing the cases operated, I will discuss the technique used. In all cases the skin was removed from the anterior surface of the thigh, where the least hair bearing surface was found. This was taken with the electric dermatome. An attempt was made to cut the graft 18/1000 of an inch in thickness in all cases. Then the skin was trimmed to fill the gap between the pharynx and esophagus. In most of the cases an Edwards Tapp arterial graft was used as the stent. The skin graft was sutured first to the remaining strip of mucosa which was nearest the mid-line in the partial pharyngectomized patients, and then to the entire circumference of the pharynx above and the esophagus below. In case of the completely pharyngectomized patients it was placed on the tissue over the anterior longitudinal ligament, sutured above to the complete circumference of the pharynx and below to the esophagus. The Edwards Tapp tube was

leveled below by removing a wedge so that it would fit better into the esophagus. After the stent has been placed so that it was well above the upper suture line, it should also extend at least one to two centimeters below. The complete closure of the graft was accomplished by suturing it to the opposite side of the mucosa in the partially pharyngectomized patients and suturing the edges of the free graft together to complete the closure in the completely pharyngectomized patients. In all instances 3-O catgut was used. The sutures were placed as close together as was necessary to close any defect and to obtain a water tight closure. The over-lying skin was then closed in the usual manner with two rows of sutures. A small drain was placed away from the graft on each side and a light pressure dressing applied. A feeding tube had already been introduced through the stent into the stomach. Eight cases were managed and repaired by the afore-mentioned technique.

The three cases of laryngo-pharyngectomy and cervical-esophagectomy will be discussed as a group. The first case was in very good condition and presented an almost complete annular lesion in the region of the cricopharyngus or slightly above. The other two cases had rather large lesions of the laryngopharynx, the pyriform sinus and extending into the esophageal area. Both were poor surgical risks having lost considerable weight as a result of dysphagia and also presented the problem of laryngeal obstruction due to the extensive encroachment of the lesion into the supraglottic larynx. In the first case and in one of the more advanced cases a tubular plastic stent was used approximately 2 cm. in diameter. Both cases developed a fistula. One had the stent removed at 14 days and the other at one month.

In the first case, the smaller cricopharyngeal lesion, the fistula closed in approximately two weeks. The patient has remained well for five years and ten months. The stent was ejected partially into the oropharynx the seventh day but was not removed until the fourteenth day as mentioned above. Though she has a small stricture which has been dilated several times (none recently), she has been able to maintain

good health by eating well masticated and pureed foods. The opening remains at about 16 to 18 F.

In the other case, a fistula developed the tenth day, but, because of the increasing size of the fistula the mold was removed in four weeks. The mold did not slip, and the fistula closed one month after the mold was removed. This patient expired six months after surgery, of cardiac decompensation. No clinical evidence of carcinoma could be seen at the time of death, although a post-mortem was not obtained.

The third case was an extremely extensive lesion involving the larynx, laryngopharynx and the cervical esophagus. The esophagus was removed down to the level of the suprasternal notch and the trachea at approximately the same level. In addition, a bilateral thyroidectomy was done *en bloc* with the laryngopharynx and cervical esophagus. This patient expired on the seventh day as a result of aspiration of vomitis. A post-mortem examination revealed that only about 30 per cent of the graft had taken. This patient was extremely emaciated and in very poor condition for surgery.

The five cases of laryngectomy and partial pharyngectomy, some with radical neck dissection, will be taken up in two groups: those without irradiation, and those with irradiation prior to surgery.

There were three cases in the first group all with large pyriform sinus lesions and direct extension beyond the cartilaginous confines of the larynx. In only one was there a metastatic gland in the upper cervical chain. All the cases were operated by total wide field laryngectomy, removal of the lobe of the thyroid gland and radical neck dissection incontinuity on the side of the lesion. In all, the lesion involved the aryepiglottic fold and extended well down to the lower limits of the pyriform sinus, so that the lower margin of excision was at the level of the lower border of the cricopharynges, thus including a very small portion of the cervical esophagus. The major part of the defect in all of these cases was approximately 8-9 cm., with only a small strip of mucosa one to one and one-half centimeters remaining connecting the esophagus with the pharynx. This was not considered ade-

quate for closure because of the great length of the defect beyond this strip of mucosa. In all of these cases a split thickness graft was draped over a three-fourth inch Edwards Tapp tube and sutured in place as described in the technique. Two of these cases recovered without surgical complications. In one a fistula developed the sixth day, when the patient drank a full glass of water. Some of it leaked around the tube and extravasated beneath the skin over the side of the neck where the radical neck procedure had been performed. It was necessary to remove the stent on the seventh day because of infection, and a fistula developed just above the tracheal stoma.

In the other two cases, without complications, the stent was allowed to remain in place for 21 days. In the case where the fistula had developed, a secondary closure was accomplished at the end of two months. All of these cases have had local recurrence: one at the end of six months, one at the end of ten months, and one at the end of one year. Swallowing was normal in all cases after removal of the stent, or when the fistula was closed in the one case. The swallowing remained good even after evidence of recurrence. Two of the cases had recurrence from involved glands in the recurrent laryngeal nerve chain or from lymphatic extension into the esophageal or tracheal area.

In one the recurrence was higher up in the pharynx. All were treated with X-rays following evidence of recurrence. Two have died of hemorrhage six months and one year after irradiation, and one is still living and free of clinical evidence of disease six months after irradiation.

In the latter group the two cases were treated with X-rays prior to surgery at the request of the patient. Both of these patients had large pyriform sinus lesions and should have been treated initially with surgery. Both had evidence of irradiation necrosis with extension of the tumor into cartilage. In both, a small strip of mucosa was left remaining, approximately one to one and one-half centimeters in width, with the greater defect approximately 8-9 cm. between the pharynx and the cricopharyngeal area. In one, a laryngectomy was

done, with a partial skin graft of the area. Infection supervened, and a large fistula developed. The stent was removed two weeks later. Pathological study of the specimen showed no evidence of tumor. The large defect after laryngectomy was necessary because of the tremendous fibrosis and necrosis which had occurred due to irradiation. This patient died seven months after surgery, due to direct extension from a metastatic gland beneath the clavicle on the right side. This became ulcerative and infiltrative, and the patient expired of hemorrhage. The pharyngostome which had developed did not close. Post-mortem examination showed no evidence of metastatic carcinoma in other portions of the body.

In the other case, a laryngectomy, removal of the lobe of the thyroid and radical neck dissection on the side of the lesion was done. The defect was larger than in the previous case, and skin grafting was done over a three-quarter inch Edwards Tapp tube, as in the previous case. A complete take of the graft occurred, it was removed in three weeks, and swallowing was normal. Two months after surgery a small fistula appeared on the side of the radical neck dissection, and a hemorrhage from the carotid artery occurred. Ligation of the artery was done above and below the rupture, and three days later this patient developed hemiplegia with marked cerebral damage. A large pharyngostome developed following surgery. At surgery it was found that the graft had taken amply but had been placed over the carotid artery, and no doubt infection in this area had supervened causing the hemorrhage of the carotid artery. The patient expired of hypostatic pneumonia several months later. Post-mortem examination showed no evidence of recurrence of carcinoma locally nor was there evidence of distant metastasis.

ANALYSIS OF CASES AND CONCLUSIONS.

A review is given of eight cases, where skin graft to the pharynx and cervical esophagus has been made either because of a complete interruptation of the pharynx with the esophagus or because of insufficient remaining strip of mucosa for adequate closure.

It is apparent that in view of the high rate of recurrence, whether it be from insufficient excision of mucosa where lymphatic spread may have taken place, or from minimal metastasis into the recurrent laryngeal chain of glands and lymphatics, a wider excision is to be considered in all future cases. Due to the fact that recent recognition of spread along nerve sheaths is a distinct possibility, the recurrent laryngeal nerve should be removed as far down as possible.

In all cases the use of 18/1000, thickness of skin was used. This is of sufficient thickness that it does not tear easily when sutured and yet is thin enough that minimum infection does not destroy the graft. A three-fourth thickness graft has been recommended by some, but it is likely that minimal infection would destroy part of the graft and contracture would be practically as much as with the thinner graft.

A good take of the graft apparently was achieved in all but two cases; one a result of extreme malnutrition and infection, although about 30 per cent of the graft did take well by the end of seven days; in the other, there apparently was no take due to irradiation necrosis and infection. Apparently the time of sojourn of the stent in the pharyngeal area does not affect the take of the graft, as those that remained only one or two weeks did as well as those which remained longer. Some have recommended that the stent remain in place six months. This hardly seems practical to me. The greatest length of time that the stent was left in place was four weeks. In two cases of complete pharyngectomy, a stricture occurred, one in which the patient lived to eat well masticated foods at the end of five years, ten months; in the other, three dilations were sufficient to maintain a good lumen until death occurred six months after surgery.

A rather rigid tube was used in the first three cases, and in one, the stent was ejected against the soft palate about 14 days. Of the latter five cases the Edwards Tapp arterial graft was used as a stent. This is completely elastic and is not rigid. The lower end must be tapered so as to fit in the cervical esophagus below the lower circumferential suture line. The Edwards Tapp tube is thought to be superior to

any other stent because of its elasticity and pliability and does not slip as easily as the smoother plastic tubes. It may be made more rigid by dipping it in Vinyl plastic. My experience with the Negus stent is limited to one case which was terminated by death, and no conclusion can be drawn.

Only four cases operated upon were good surgical risks, yet the operative mortality rate was only 15 per cent. While this is relatively high it does not seem extremely so when considering the condition of these patients at the time of surgery.

Finally it must be admitted that skin grafting for the preservation of an ample tube for swallowing in cases of partial or complete laryngo-pharyngectomy and cervical-esophagectomy is not without its complications and hazards. It seems quite apparent that there was less hazard and fewer complications when the general condition of the patient was good and little or no evidence of stricture when a small strip of mucosa was left, supplemented by the skin graft.

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THE PROCUREMENT AND PROCESSING OF ENDOSCOPIC BIOPSIES.*

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The closest cooperation between endoscopist and pathologist is essential if maximum information is to be obtained from endoscopic examinations. The endoscopist in the practice of his specialty requires, probably more than any other specialist, the technical services and the professional opinion of the pathologist. The purpose of the endoscopic examination is largely for diagnosis. This means that all secretions and biopsy tissues taken from the air or food passages during a laryngoscopy, bronchoscopy or esophagoscopy must be processed for microscopic examination by the pathologist. The small volume of the secretions and the limited size and total amounts of the biopsy tissues establish restrictions in the processing techniques. Stated in another way, the processing procedure must conserve all of the secretions or tissues obtained by the surgeon, and safeguard them against loss, especially of a solitary particle that may have diagnostic value. Limitations as to the size and amount of biopsy material obtainable are due to several factors. The anatomical limits of the surgical field available to the peroral endoscopist necessitates employing small instruments which often can, at best, procure only fragments of tissue or a few cubic centimeters of significant

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secretions; furthermore, the lesion itself may be small in total volume. Its complete removal with a surrounding area of apparently normal tissue, favorable for histologic diagnostic studies, may permanently impair function should the lesion be benign. This is particularly true of laryngeal biopsies in the so-called border-line lesions of keratosis or leukoplakia when an adequate biopsy following a previous procedure and a report of "insufficient tissue," may result in permanent hoarseness; nevertheless, satisfactory results are realized when endoscopic techniques are closely integrated with the processing procedures required for the preparation of the secretions. The following work arrangements between the

Fig. 1. Bronchoscopic aspirator with centrifuge collecting tube. Straight or curved flexible aspirators and straight open-end tips are interchangeable.

bronchologist and the pathologist have been used with advantage for many years.

Secretions.

Secretions are aspirated directly into an ordinary, tapered 15 cc. glass centrifuge tube. The aspirators are so constructed that the material can be drawn into the centrifuge tube through a two-hole rubber stopper onto which the tube is fastened with a clamp (see Fig. 1). A thumb valve on the aspirator permits intermittent suction and allows release of suction should the tube suddenly fill with secretions, thus avoiding loss of material into the suction apparatus. Straight or curved rigid or flexible aspirating tubes of appropriate size may be attached to the collecting tube. This collecting

system is simple, efficient and sufficiently variable in size to permit its use in any of the peroral endoscopic examinations, whether the patients are adults or children.

Generally, the first specimen obtained is sent to the laboratory for bacteriologic study. The centrifuge tube is removed, and a second tube is fixed to the two-hole stopper of the

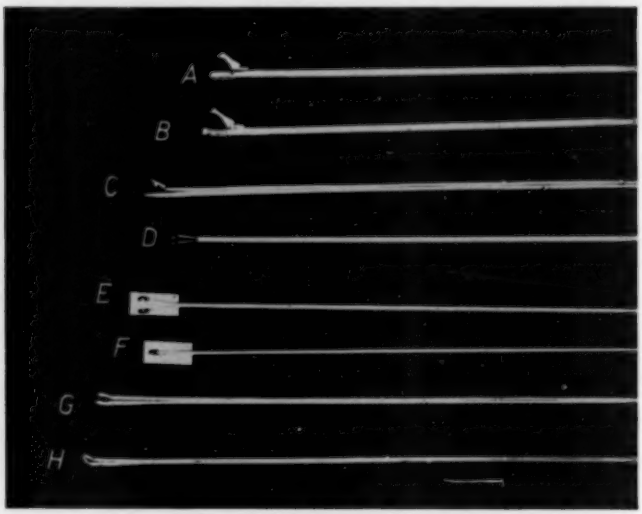

Fig. 2. Endoscopic biopsy forceps. The small size of the biopsy tissues requires special processing in order to preserve every fragment for histologic analysis.

aspirator and another specimen is collected which will be processed for histologic examination. A saline wash of the bronchus may be necessary if there is insufficient secretion for the second collecting tube. On completion of the endoscopic examination, Zenker's solution* (or other fixative solution) is added to the second tube, the solution being drawn through the aspirator in order to include any residue in the

*Zenker's solution (without acetic acid): Distilled water, 1,000 cc.; mercuric chloride, 50 grams; potassium dichromate, 25 grams; sodium sulfate, 10 grams.

laboratory specimen. Both tubes are closed with rubber stoppers, and a strip of surgical tape with the name of the patient is attached to each tube and the tubes with the requisitions are sent to the laboratory.

The handling of the specimen for bacteriologic examination is rather standard, with smears, cultures, sensitivity determinations and animal innoculation or special fungus studies requested according to the clinical needs of each patient. The contents of the second aspiration collecting tube are processed as biopsy material in the manner described below, for cell-block study.

Biopsies.

Each endoscopist has his own preference in regard to biopsy forceps (see Fig. 2). For verrucous tumors almost any forceps will give adequate, representative tissue. The straight and angulated cup forceps of appropriate length (see Fig. 2; G, H) and the globular-objects foreign-body forceps (see Fig. 2; D, E, F) are most commonly used. Cutting biopsy forceps require frequent adjustment and sharpening, and these must be used in tougher, fibrous tissues (see Fig. 2; A, B, C). Their construction should be such that the cutting blades continue into the angle of the jaws of the forceps to prevent leaving a strip of uncut tissue in the closed jaws. Basket types of forceps have the advantage of reducing the tissue crushing action of forceps with solid blades. The small telescopically guided forceps are still not entirely satisfactory, but positive biopsies can be obtained if all of the fragments of tissue collected in these tiny blades are preserved.

Routinely, particles of biopsy tissues are placed at once in a tapered 15 cc. centrifuge tube (see Fig. 3). A cubic centimeter of saline solution can be placed in the tip of the tube to aid in releasing the tissues from the instrument. Zenker's solution (or other fixative solution) is added in sufficient amounts, the tube is stoppered, labeled properly and sent to the laboratory. Zenker's solution precipitates the formed and dissolved tissue elements in the secretions and properly fixes the biopsy tissue particles.

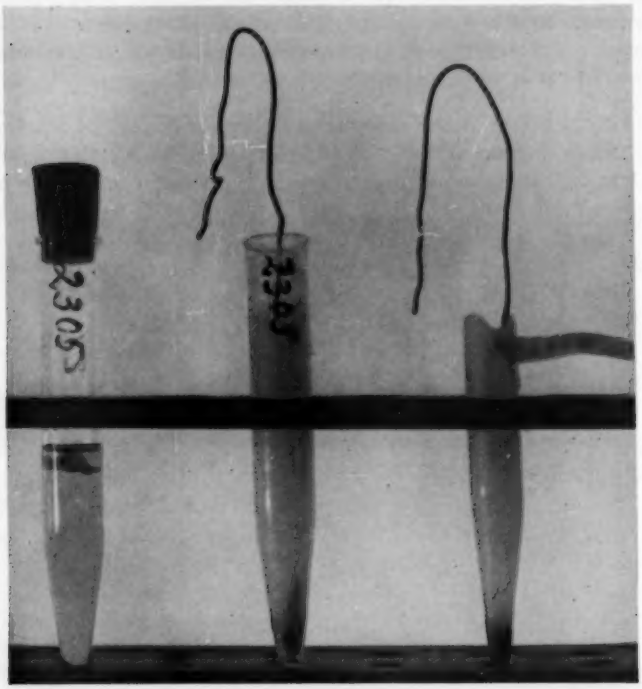

Fig. 3. Three steps in processing small endoscopic biopsies. Left—The biopsy in Zenker's solution in the centrifuge tube. Center—The specimen centrifuged, covered with paraffin into which copper wire had been inserted to facilitate handling. Right—Button of biopsy material at bottom of paraffin column which will be embedded in block for cutting. All tissue fragments obtained are included in the button.

Zenker's solution is preferred to other fixatives such as 10 per cent formalin for two reasons: first, the formalin has a tendency to shrink tissues, and a significant loss of detail may be associated with its use in handling the small bits of endoscopic biopsy material; second, in unusual tumors requiring further histologic staining and study (see Fig. 4), tissues fixed in Zenker's solution permit more favorably such further investigation, whereas those fixed in formalin may no longer be suitable for this further processing.

After two or three hours' fixation, these precipitates or tissues are collected by centrifugation in the tip portion of the tube and the fixative solution is decanted. The entire process of dehydration, clearing and paraffin embedding is carried out in the original centrifuge tube. After each change of water (for washing), 70 per cent alcohol, 80 per cent alcohol, 95 per cent alcohol, two changes of absolute alcohol, two changes of xylol or toluol, the secretion precipitates or tissues

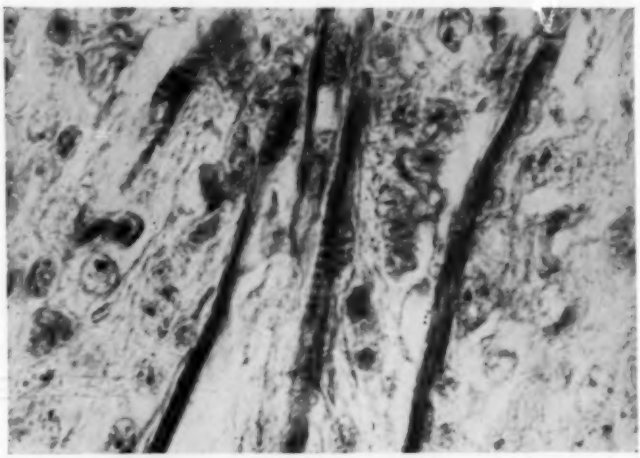

Fig. 4. Rhabdomyosarcoma of the larynx of a five-year-old boy. The advantage of Zenker's fixation over formalin is demonstrated in this photomicrograph of Zenker's fixed tissue.

are collected in the tip portion of the tube by centrifugation, and the solutions are decanted. Finally, melted paraffin is added to the tube and the infiltration of the precipitates and tissues with paraffin is carried out by placing the tube and its contents in a paraffin oven. Two changes of paraffin suffice. A short piece of flexible wire (copper) with a loop at the end reaching into the melted paraffin is hung over the lip of the centrifuge tube, and the tube is cooled to harden the paraffin. Then the tube is dipped quickly into warm water and by means of the wire, the column of paraffin is

drawn out of the tube. The short cell-block button of infiltrated tissues at the tip is cut off, is embedded in melted paraffin, cooled and blocked for sectioning. The secretions are cut serially, enough to cover at least five slides, stained with hematoxylin and eosin and mounted for microscopic examination.

In using this collecting and processing technique described, all of the secretion precipitates and the biopsy tissues are

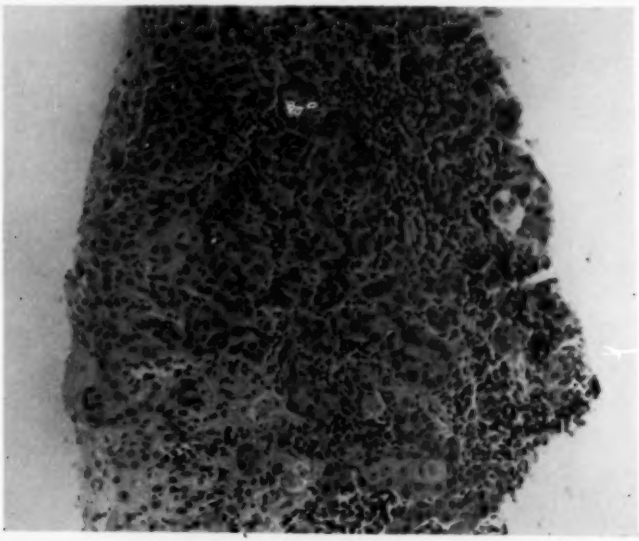

Fig. 5. Photomicrograph of bronchogenic carcinoma tissues obtained by aspiration technique. There was no visible tumor tissue obtainable by forceps biopsy.

conserved without loss, even to the smallest particle which alone may be the important tissue for diagnosis (see Fig. 5). The pathologist or his technician does not have to strain out small strands of tissue from the comparatively large volume container often supplied by the laboratory to the operating room. Loss during transfer is eliminated. Most important, tissues in aggregates of cells are collected by the aspirator.

This gives a morphologic pattern often of more diagnostic significance than cytologic smears and improves the percentage of positive biopsies in lesions in which the endoscopic findings are equivocal.

SUMMARY.

A simple, practical method of collecting and processing endoscopic secretions and biopsies is described. All diagnostical material is aspirated or placed directly into centrifuge tubes that are sent to the laboratory without transfer. Bacteriologic studies are made from the contents of the first tube. Histologic studies are made from the centrifuged contents of the second. The preservation in this manner of even the smallest particle of tissue which may be of diagnostic significance is possible. The advantages of various types of biopsy forceps in securing tissue and Zenker's solution as a fixative are discussed.

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HUMBOLDT UNIVERSITY OF BERLIN (CHARITE).

The celebration of the 250th Anniversary of the Charité will be held in Berlin from November 6-19, 1960, in connection with the 150th Anniversary of the Humboldt University.

Applications for participation are to be directed to the Committee for the Preparation of the 250th Anniversary of the Charité, Berlin N 4, Schumannstrabe 20-21, c/o Dozent Dr. med. habil. Dagobert Müller, secretary of the committee.

EVALUATION OF TREATMENT IN EXTERNAL EAR INFECTIONS.*

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External ear infections present a dual challenge to the otologist. The immediate problem is the relief of pain and then the careful study of the cause and prevention of future episodes. To accomplish this, an understanding of the anatomy and physiology of the canal is imperative. Meticulous laboratory tests may be necessary, including cultures, sensitivity tests, biochemistry (including blood sugar, P.B.I.) and in selected cases, biopsy. This should be correlated with a painstaking history in an attempt to identify the etiologic trigger. These basic factors are frequently overlooked in our eagerness to try out new drugs with which clinical experience may be minimal and pharmaceutical propaganda maximum.

The external canal is a test tube of skin closely attached to the underlying structures of cartilage and bone with little subcutaneous tissue present; the outer one-third contains a complex system of glands that secrete cerumen and are the key to the door of the canal. Their secretion is a mixture of secretory products of two types of glands found in the cartilagenous portion; sebum (from sebaceous glands) and aprocrine sweat (from the cerumenous glands); the factors that control this production are not known, but some drugs, emotions, temperature variations, and mechanical irritation stimulate the smooth mucle fibers that produce contraction of the glands and make them secrete more than normal. The amount and character of the cerumen seems to vary in different races and certainly in different individuals.

In reviewing the literature, it is interesting to find that the Japanese Navy[4,5] had done a great deal of research on

*Read at the meeting of the Southern Section, American Laryngological, Rhinological and Otological Society, Inc., New Orleans, La., Jan. 15, 1960.

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cerumen. In selection of submarine personnel, it is quite important that body odors be controlled and it is known certain types of cerumen emit unpleasant odors. This may be due to certain types of bacteria acting upon the cerumen. There is a racial and individual difference in this respect. The function of cerumen has many theories: as a coating, trapping foreign matter that might enter the canal, also carrying with it epithelial scales and hairs out of the meatus. It may prevent dessication of the skin and makes it pliable. The antibacterial and fungicidal properties are debatable. It is composed of amino acids, potassium, sodium, calcium, magnesium, phosphorus, sulphur, silicon, cholesterol, cerotic acid and neostearic acid and consistently has an acid pH. Recently we ran cultures from the external ear of 50 individuals who had never had ear infections of any type. The cultures were taken under aseptic technique, the results of which showed bacteria of two groups: the micrococcus and diphtheroids. These findings are quite consistent with those of other investigators.

Cutaneous sensibility in the canal does not seem in any way peculiar. Normal response to touch, pain, hot and cold are present, although there seems to be an increased sensitivity to itching at the entrance of the canal. The relationship of the autonomic nerves to the cerumenous-gland tubules has been demonstrated. Stimulation of the cerumenous glands can be caused by andrenergic drugs such as epinephrine[7]; emotions such as anxiety and fear; mechanical irritation such as scratching, and in climatic temperature variations, bearing in mind that the pilo-sebaceous ear glands are really modified sweat glands.

If one understands these anatomical and physiological concepts, he becomes better prepared to approach therapy of the canal; even then it may impose anatomical and physiological peculiarities that will tax his ingenuity to the utmost and restrict the type of therapy used. It is an impossible and endless task to review all the therapy advocated in the literature, so general therapeutic rules must be followed. It might be interesting to note the drugs advocated three decades ago and compare them to those currently in vogue. Among those

used in the early thirties[3] were thymol, iodine, cresatin, merthiolate, mercurochrome, salicylic acid, boric acid, sodium borate, either alone or combined with alcohol. The fungus ear was quite the thing. This era existed for many years. Then the pseudomonas appeared on the scene and distorted the picture quite as much as the aspergillus.

Research conducted and initiated by the Air Force in World War II at Randolph Field[2,6,8] paved the way for a better understanding of the condition. Extensive investigations including biopsies of the external ear were done. We were reluctant to do this except on very special occasions, but with the advent of antibiotics and increased liability insurance, we were bolder in our approach. From this work has come basic rules of therapy as they apply to the external ear today. In general, the more acute and inflammatory the dermatosis, the milder the medicament. Cresatin[1] which we advocated years ago, now is used only occasionally, because of the sensitivity it produced. The sheltered skin of the ear canal is very susceptible, and one must be extremely discreet in handling it. Careful and meticulous cleansing is paramount whether it is done by irrigating with hypertonic solution, applying suction with a fine cannula, or by a stream of gently blown compressed air. Therapy should be initiated with minimum effective concentration of the drug selected and over-treatment must be avoided; this is a very common mistake. Dryness of the canal is the keynote to success in preventing recurrences. Systemic therapy is a must in many cases, such as the administration of thyroid, regulation of diabetes, and most important, control of nasal allergy. Eosinophils in nasal and pharyngeal secretion are of great diagnostic value. Bacterial and fungous infections are not often the primary etiologic agent but accompany other causative factors. Antibiotics in combination with cortico-steroids are valuable when used topically. It was stated at the Seventh Annual Antibiotic Symposium that innumerable synthetic penicillins were possible, more than 200 have already been prepared. New antibiotics are constantly appearing, such as Declomycin (DMCT), Colistin, Refomycin, Asparomycin, Griseofulvin, and Streptozotocin.

The external ear has a high index of epidermal sensitivity and because of this, most of the antibiotics in ear drops have a very low rate of anaphylaxis. Penicillin and sulfonamides frequently produce reactions while neomycin and polymyxin seldom do so. The choice of antibiotics should be influenced by direct smears, cultures and sensitivity tests. Once the bacterial infection is controlled, antibiotics should be discontinued and the situation re-evaluated. The micro-environment of the infection in the host should be carefully studied. This should include the predisposing factors such as heat and humidity; trauma, allergy; diabetes, overweight; thyroid imbalance; daily habits and emotional problems. The occasional use of staphlococcus toxoid may be helpful in preventing recurrence of circumscribed otitis externa (furunculosis). The use of Roentgen ray locally occasionally is of value in relieving itching and pain.

The public is better informed on the wonder drugs because of the publicity given to them in poular magazines and television. This has caused the individual to lose fear of infection; he generally thinks the wonder drugs will do the job in protecting him. As a consequence of this attitude, respect for the medical profession has deteriorated somewhat as the reliance on the newer drugs increases. Although there is an increasing danger that the chemotherapy of infection is approaching the ultimate, I believe we are on a firm footing in our treatment of ear infections if we do not lose perspective. Too often we are prone to give antibiotics credit for a cure when other factors have accomplished it.

In the foregoing remarks I have given you some of the ideas of treatment and some of the drugs that have been used over the last three decades. It started with simple clinical observations and has grown into a more detailed examination that includes more meticulous laboratory studies. We must not lose sight of the fact that we are the doctor supervising the treatment of the patient and the otologist should still be the one to handle this type of infection.

SUMMARY.

1. Predisposing factors must be considered in external ear

infections; correction of systemic faults may accomplish more than local therapy.

2. The ear canal must be kept dry, clean and protected.

3. Laboratory reports must be interpreted only in light of clinical data.

4. The ear infection should be managed by the otologist.

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Suite 14, Medical Center.

SIXTH INTERNATIONAL CONGRESS ON DISEASES OF THE CHEST.

The Sixth International Congress on Diseases of the Chest will be held at the University of Vienna from August 29 to September 1, 1960.

LARYNGEAL TRAUMA.*†

TRUETT BENNETT, M.D.,
(By Invitation),
Atlanta, Ga.

Serious trauma to the larynx is fortunately infrequent, possibly because of the protection offered by the mandible and because of its mobility and elasticity. The majority of cases are caused by automobile accidents and are associated with multiple injuries, especially in the maxillo-facial area and intracranially. It would be interesting to know the incidence of crushed larynges in fatal automobile accidents, but I have been unable to find statistics on this. In the typical case, the immediate problem of respiratory difficulty is solved by a tracheotomy, and the larynx is then forgotten in preference to treating the other injuries. Several weeks later, difficulty in decannulating the patient arises, by which time the problem of a chronic stenosis is established, and a lumen has to be created through a deformed larynx and mass of scar tissue with only compromising results. Early definitive treatment will in most cases prevent these chronic problems and offer better results in regard to the voice and airway than treatment after a stenosis is established.

In general, the injuries to the larynx and trachea from external trauma may be grouped as: *1.* lacerations and stab wounds, *2.* crushing injuries, and *3.* loss of substance by avulsion or gun blast, etc. The initial symptoms are dyspnea and hoarseness. These may be obvious at first or may develop gradually over a period of a few hours. There will usually be some dysphagia from edema in the hypopharynx. There may also be hemoptysis and swelling of the neck from subcutaneous emphysema and ecchymosis. Severe damage to the larynx occurs in some cases without visible damage to the skin of

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the neck, so that absence of discoloration or abrasions may offer false reassurance.

The lumen of the larynx and trachea depends upon the integrity of the cartilaginous framework; therefore, it is obvious that when there is fracture of the cartilage and overlapping of the fragments, the lumen will be decreased. There is the additional factor of chondritis which further deforms the framework and of scar tissue resulting from torn mucous membranes and hematoma which stenose the lumen sometimes to complete closure. Cartilaginous fractures in general become increasingly difficult to reduce after 48 hours because of the rapid development of fibrous tissue and the difficulty in freeing the cartilage fragments from it. When the average case reaches the otolaryngologist for definitive treatment, about six weeks have elapsed and any possibility of manipulating the cartilage fragments is gone.

TREATMENT.

In case of the recently traumatized larynx, the situation will usually be obvious and the need for immediate heroic measures plain. A tracheotomy is, of course, the first need as a rule, and this should be as low as possible. If, for the sake of expediency, a cricothyroidotomy is done, an elective tracheotomy should be done within the next few hours. Respiratory obstruction sometimes develops after a few hours from inflammatory edema, and thus all neck injuries can be potentially a danger to the airway, although it may not be obvious at first. If there is any obstruction to the airway early in the course of events, a tracheotomy should be contemplated, because the obstruction can be predicted to increase some over the next 48 hours; also, a properly done tracheotomy will minimize subcutaneous emphysema and the possibility of thoracic complications.

In case of an open wound of the larynx, careful cleansing and accurate approximation of the parts are important. Cartilage fragments should not be removed if at all possible to support them adjacent to a blood supply. If there is any possibility of stenosis later, a mold of some sort should be

inserted.[1] A rubber core mold would serve the purpose but would have to be changed frequently. An acrylic reproduction with a lumen drilled in would be preferable. This should be kept in for about six weeks.

When there is a closed crushing injury to the larynx, as determined by respiratory obstruction, findings of hematoma, etc., one can be certain that there will be a cicatrical stenosis later unless preventive steps are taken early. An adequate preventive measure may amount to no more than exposing the larynx in direct laryngoscopy and inserting an acrylic mold as described above. If the injury is severe, it may be wise to do a thyrotomy, mold the cartilage fragments in place and secure an acrylic stent in place by tantalum wire. For successful results, it is important to do this as early as possible, preferably within the first 48 hours.

A chronic stenosis may be the end result of the trauma and presents a more complicated problem. Attempts at overcoming chronic stenosis of the larynx probably began with Dr. L. Von Schwetter of Vienna in 1871 when he devised methods of dilatation using metal olives and rubber tubes.[2] O'Dwyer described his method of entubation in 1885. Open operations were also done in those early days and a method of treatment involving a laryngo-tracheostomy and dilatation of the stricture under direct vision was presented by John Winslow. The core-mold method of Jackson was a great development and with sufficient patience, almost any stricture can be cured by this method. Schmiegelow[3] began doing the open operation with excision of scar and insertion of rubber tube stents in 1910 and in 1929 reported 18 successful cases. Shortly thereafter, Arbuckle[4] first reported the use of skin grafting and since then there have been important modifications reported by Negus,[5] Figi,[6] Erich,[7] and LeJeune and Owens.[8] Woodward[9] has described a single-stage method which has been successful in several cases in which he excises the stricture and uses a free graft of bone from the body of the hyoid between the alae of the thyroid cartilage. He then inserts an acrylic reproduction of an O'Dwyer tube into the lumen and secures it there by wire.

On the cases that we have encountered, we have been discouraged with dilatation and with the use of plain polyethylene tubing inserted as stents, but we have had success with Woodward's method of using a hyoid bone graft and acrylic mold and with the use of skin grafting, using a sponge rubber mold to hold the graft in place as described by Figi and modified by Erich.

Most cases are best treated by an external approach. If a tracheotomy is not already done, it should precede the corrective surgery and be placed as low as possible. If it was originally too high, it may be necessary to lower it. A general anesthetic may then be given and a thyrotomy done. If the stricture is not too long, skin grafting will not be necessary. As a rule, after excision of the scar tissue and webs, there will still be insufficient airway due to distortion of the cartilages, in which case we prefer to use the hyoid bone graft as described by Woodward. An acrylic tube fashioned after an O'Dwyer entubation tube is inserted and secured in place by tantalum wire. A central segment of the hyoid bone is then excised and after being fashioned to proper size is sutured between the alae of the thyroid cartilage or between the cut ends of the cricoid as the situation demands. Small holes are drilled in the edges of the graft to hold the sutures.

Acrylic stents and molds can be made by any good dental laboratory if they are provided with a model. It is very important to specify that a lumen be made, as this adds greatly to the comfort of the patient. They rarely cause any reaction and will usually be tolerated as long as is necessary.

For the very extensive strictures, especially when the trachea is involved, the skin grafting technique as described by Figi and Erich is an appropriate solution. If this type of operation is necessary, the tracheotomy should be large and at least 1 to 2 cm. below the stricture. The stricture is exposed by a mid-line incision through the larynx and trachea and is excised. A split thickness skin graft is then obtained and sutured around a cylindrical piece of foam rubber sponge with the raw surface outward. This is then inserted into the area of denuded epithelium and held in place by heavy silk

sutures that go through the rubber mold and are tied externally across the skin incision. A heavy silk suture is also placed through the sponge rubber and brought down through the tracheostomy to be tied to the tracheotomy tube. After ten days, the foam rubber mold is extracted through the tracheostomy. A model for an obturator is then constructed out of an appropriate size rubber tube and dental compound. This obturator must have a lumen, fit into the grafted area, and have a lip that protrudes out through the tracheostomy and still leaves room for a tracheotomy tube. After the model is constructed, the sponge rubber is inserted through the tracheostomy back into its original place until a dental laboratory can construct the obturator in acrylic. After this is obtained, the rubber mold is again withdrawn and the acrylic obturator inserted into its place. It should be left in place for at least six months, and usually this may be done without discomfort or need for special care. If the lumen is still adequate after the obturator is withdrawn, the tracheotomy may be closed. If the tube is left out for about a month, the stoma will close partially and then require only a simple procedure to finish closure. Occasionally, the stoma will be so large as to require multiple stages in order to close it.

Sometimes one finds the trachea completely separated from the larynx and it has to be mobilized and anastomosed. An acrylic stent should be used to prevent stricturing at the anastomosis.

Each case presents a different problem, and it is difficult to follow a set routine on each one. There are many other methods in which the surgeon should be versed in, in order to cope with any situation, and some degree of *"ad libing"* is required in each case.

CASE REPORTS.

Case 1. A 23-year-old male had worn a tracheotomy tube and had been unable to get any air through his larynx since an automobile accident three years previously. He was referred to the Ponce de Leon Infirmary where examination and X-ray showed a complete stricture at the cricoid and upper trachea and a bilateral paralysis of the vocal cords. The tracheostomy was enlarged and the larynx opened. A complete stricture was found with destruction of the anterior half of the cricoid, and loss of at least one tracheal ring. The trachea was dissected free downward,

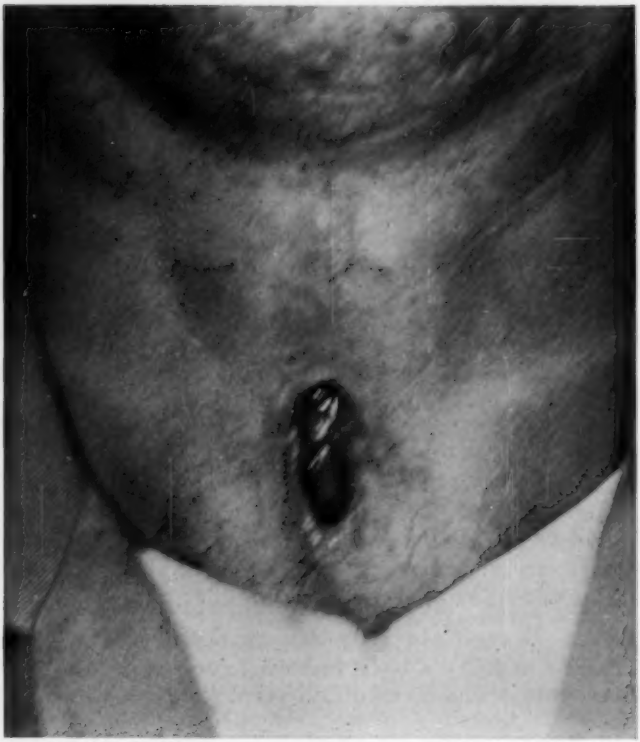

Fig. 1-a.

brought up and anastomosed to the remainder of the cricoid. A section of the hyoid was grafted to bridge over the defect in the cricoid, and an acrylic stent was secured in place by a tantalum wire. He was able to talk for the first time in three years. After about six weeks he coughed up the acrylic mold. The lumen shrank down as would be expected and on reopening of his larynx about two months later he was found to have an epithelized lumen about 4 mm. in diameter. This was a big improvement on his original state, however. The Erich technique of skin grafting was then done after the scar tissue was excised. To try to avoid the necessity of an arytenoidectomy later for the paralyzed vocal cords, a portion of the vocal cords was removed submucosally, and the acrylic obturator was constructed long enough to fit between the cords. After six months the obturator was removed. He had a good lumen, and the vocal cords remained fixed in abduction. The large tracheostomy was closed in one stage with inversion of the skin about the edges and a sliding flap. A check-up one month later showed a good airway, and he

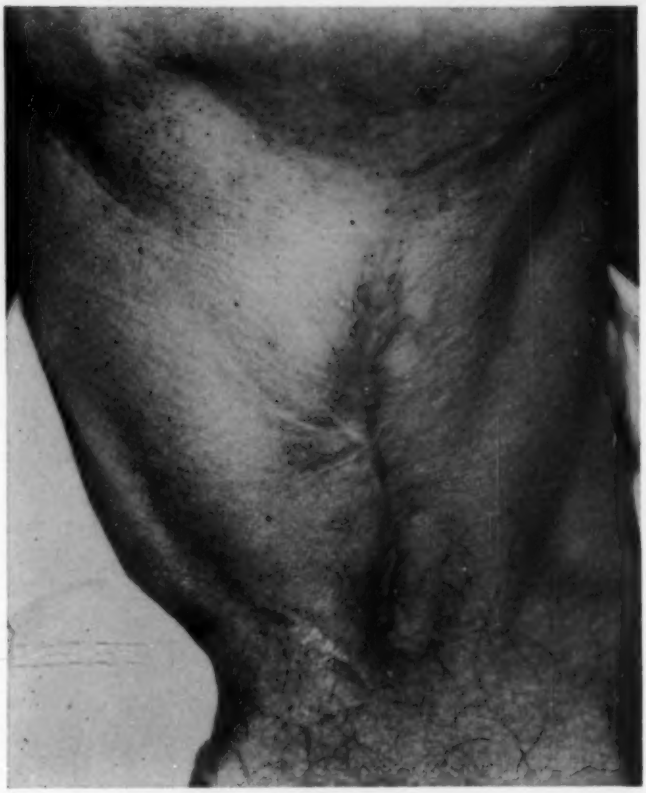

Fig. 1-b.

Fig. 1. a. and b. This large tracheostomy was closed by inversion of skin edges and a rotating flap.

had resumed his job of brick-laying. He was decannulated about three years ago, and a recent communication revealed that he was still doing fine.

Case 2. A 45-year-old woman had several procedures done for correction of a bilateral abductor paralysis of the vocal cords. She developed adhesions between her vocal cords and remained dependent upon her tracheotomy. A thyrotomy was done, the adhesions divided, and the Woodward technique of grafting a piece of hyoid bone between the alae of the thyroid cartilage and leaving an acrylic stent in the lumen was done. The stent was removed after six weeks and she was able to be decannulated a month later. Four years after surgery, she is still able

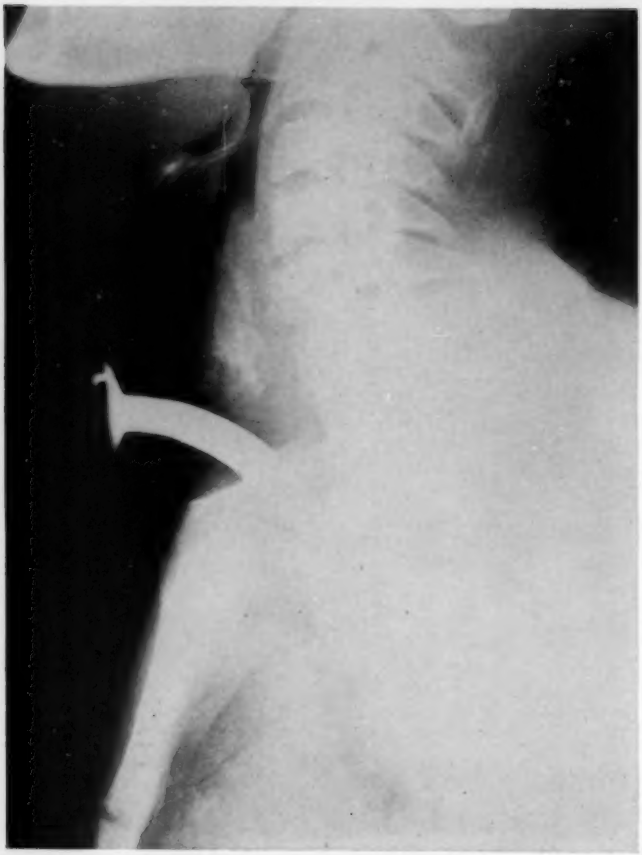

Fig. 2. X-ray showing acrylic obturator in place (Case No. 1) after skin grafting.

to do well without a tracheotomy. I believe she would have more lumen, however, if the stent had been left in place longer.

Case 3. A 35-year-old female had remained dependent upon a tracheotomy three months following an automobile accident. A thyrotomy was done, and there was found to be diminished AP diameter presumably due to fracture of the cartilages. The lumen was increased by using a bone graft between the alae of the thyroid cartilages and an acrylic stent was left in place. After two months, the stent was removed endoscopically. She developed a cutaneous fistula and granulation tissue in the anterior

commissure which promptly subsided after removal of a small sequestrum of bone by laryngoscopy. She was then decannulated and the tracheostomy allowed to close spontaneously. Three years after surgery she does well except for some dyspnea on exertion.

Case 4. A 21-year-old male had a severe injury to his neck in an automobile accident—a deep transverse laceration involving the larynx and pharynx was reportedly present. This was closed primarily, and a tracheotomy was done. A sub-dural hematoma and multiple fractures prevented further attention. We saw him about six months after the injury, at which time the tracheotomy was closed up, but he was having a good deal of dyspnea on exertion and a very poor voice. Examination showed him to have a markedly decreased glottic lumen with distortion and projection of a sharp ledge into the lumen. A tracheotomy was done, and the larynx was opened up. The projection visible on mirror examination was found to be caused by a piece of cartilage. This was excised and a section of hyoid was removed and grafted in between the alae of the thyroid cartilages after an acrylic stent was secured in place within the lumen. The acrylic stent was removed via laryngoscopy six months later, and he was decannulated a month later. He is much improved, but still cannot do heavy labor; however, he is able to do the job that he was trained for and is doing well.

Case 5. An 18-year-old female was involved in an automobile accident about two years ago and required a tracheotomy. She was referred to the Ponce de Leon Infirmary about six weeks later when decannulation was found impossible. Her pathology seemed to be limited to the area of the glottis in the form of posterior webbing and some decrease in AP diameter. A hyoid bone graft was done and an acrylic stent left in place for six months. She was decannulated, but a tracheotomy had to be done again three months later because of progressive dyspnea. She has had several dilatations with some increase in lumen, but this could not be done often enough to be effective because of her living out of town. A medium-size acrylic reproduction of an O'Dwyer tube was inserted per laryngoscopy and left in place four months. This was then replaced with an acrylic reproduction of a No. 38 core-mold with a lumen drilled through it for two more months. This was removed only recently. Communication by telephone revealed that the airway is greatly improved so far; however, she is pregnant, so decannulation will not be considered for a few months. If the posterior webbing re-forms, she will need skin grafting.

SUMMARY.

A discussion of the immediate and late effects of external trauma to the larynx, and recommended treatment has been presented. Case reports representing a variety of situations are given. Practically any chronic stricture can be corrected if the surgeon is persistent, but the end results are much better if the stricture is prevented by early definitive treatment. This should be done within the first 48 hours if possible.

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144 Ponce de Leon Avenue.

COURSE IN LARYNGOLOGY AND BRONCHOESOPHAGOLOGY.

October 17-29, 1960.

The Department of Otolaryngology, University of Illinois College of Medicine, will conduct a postgraduate course in laryngology and bronchoesophagology, October 17-29, 1960, under the direction of Paul H. Holinger, M.D.

Registration will be limited to 15 physicians who will receive instruction by means of animal demonstrations and practice in bronchoscopy and esophagoscopy, diagnostic and surgical clinics, as well as didactic lectures.

Interested registrants will please write directly to the Department of Otolaryngology, University of Illinois College of Medicine, 1853 West Polk St., Chicago 12, Ill.

CYSTIC LYMPHANGIOMA OF THE PAROTID REGION.*†

RALEIGH E. LINGEMAN, M.D.,

Indianapolis, Ind.

Cystic lymphangiomas are multilocular cystic tumors of a benign neoplastic nature which have a lymphatic origin and whose spaces are lined with a single layer of endothelium. These tumors have the power of new growth and infiltration of surrounding structures by local extension. This definition includes cystic hygroma which is considered to be an identical pathologic process. Approximately 93 per cent of the reported cases in the literature are located in the cervical region, although these tumors have also occurred in the axilla, groin, popliteal fossa, retro-peritoneal space and mediastinum. Primary involvement of the parotid area without associated involvement of the cervical region appears to be a very unusual occurrence. A review of the literature on this subject, which has been published during the past 45 years, revealed only an occasional case of primary parotid involvement by these tumors; consequently, it is felt worthwhile to describe five cases with which the author has had experience during the past four years.

The earliest report in the literature was made by Redenbecher in 1828, although the first important contribution to our knowledge of hygroma was made by Wernher in 1843. He was the first to name these tumors cystic hygromas. He recognized that most of these tumors occurred in the cervical region, and he believed that they were the result of a new formation independent of the development of the fetus. Bruch opposed the idea of Wernher; he felt that there was no evidence of neoplastic tissue in cystic hygroma, but rather that these lesions respresented a hydrops of the subcutaneous

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†From the Department of Otolaryngology, Indiana University School of Medicine.

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tissues. Rokintansky believed that this tumor resulted from a tissue limiting process around an area of edema or serous exudate occurring in the fetus. The limiting walls were formed from the thickened pre-existing connective tissue which surrounded the fluid. The lining of the walls subsequently became smooth whereupon a secretory balance occurred between the walls and the fluid. Gurlt agreed with Rokintansky and referred to the condition as hydrops universalis. Virchow in 1863 agreed with Wernher that hygroma represented a new formation and was unrelated to developmental anomalies of the fetus. Arnold in 1865 reported two cases of cystic hygroma and stated that the growths did not arise from intracarotid ganglia since the cystic cavities were lined with endothelium. His conception of the growth was that the cellular elements of connective tissue disintegrate forming cystic spaces in which fluid accumulated secondarily. Koester demonstrated the endothelial lining of cystic hygroma by the means of silver solutions, and he concluded that the cystic cavities of hygroma arose by widening of pre-existing lymph vessels. He thought that this accounted for the penetration of those tumors into surrounding organs and tissues, and he designated the hygroma tumors as lymphangiectasis congenita. Brost, in 1902, made an extremely important observation. He studied lymphangioma located within lipoma and offered evidence of the formation of new lymph capillaries from the intra-cellular canalization of beds which sprouted from the endothelial lining of the dilated vessels.[6] Dowd[4] reviewed the literature up to 1913 and reported 91 cases of cystic hygroma occurring in the neck and 35 cases of hygroma located in the axilla. Dowd also quoted the work of McClure and Sylvester in 1909 concerning the embryology of the lymphatic system. They were of the opinion that hygromas arise from sequestrations of lymphatic tissue derived from the primitive jugular sacs. Dowd also thought that these lymphatic rests possessed an independent power of irregular growth. Ribert thought that the growth of the hygromas and lymphangiomas was similar and the result of independent power of penetration on the basis of endothelial shoots which later became canalized and thus would give rise to cysts. He also agreed with Dowd

that hygromas are derived from the lymphatic sequestrations which are remnants of the primitive jugular sacs.

EMBRYOLOGY OF THE LYMPHATIC SYSTEM.

The generally accepted facts concerning the development of the lymphatic system have resulted from investigations and observations of Sabin, Huntington and McClure. They

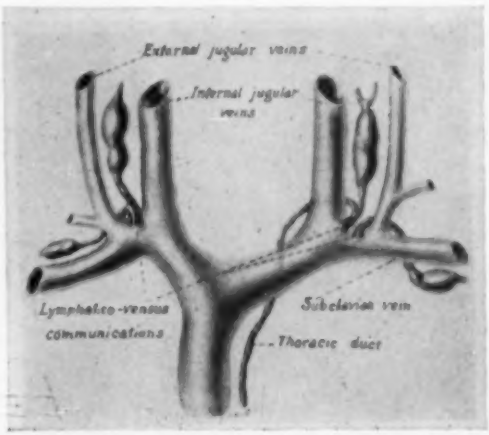

Fig. 1. Reconstruction of the jugular sacs of an 11 millimeter cat embryo showing the relation of the lymphatic buds to the jugular and subclavian veins through which the adult communications are established (after McClure and Sylvester).

have established that in the primary stage of development, a capillary plexus is formed from the jugular vein on each side. In certain areas a part of the capillary plexus is cut off from the parent vein. This group of isolated spaces lined by endothelium remains for a short time constituting the anlage of the lymphatic system. These isolated capillaries then dilate and coalesce to form symmetrical, lined sacs. In this manner the two primitive jugular sacs, one on each side, are formed (see Fig. 1). The thoracic duct connects the pelvic and retroperitoneal sacs with the left jugular sac and then forms an opening into the veins at the jugular valve. On the right,

there is a somewhat similar development. Another pair of lymph sacs appears in the pelvis which are related to the corresponding iliac veins into which they open. The secondary stage of development then involves the peripheral growth of the lymphatic vessels. Sabin has shown that this is accomplished by endothelial sprouts which are derived from the lining of the jugular sacs which in the third month, spread and invade the tissues of the neck, head, and arm. From the

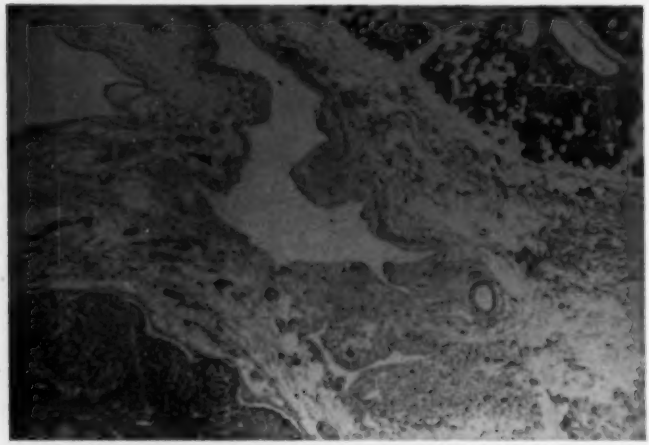

Fig. 2. Cross section of a cystic lymphangioma of the parotid area showing the cystic spaces lined with a single layer of endothelium together with lymphoid and glandular tissue.

pelvic and iliac sacs, outgrowths penetrate the hind limbs and the tissues of the pelvis and buttocks. In addition, there is the element of secretion from the endothelium of the newly formed lymphatics. This is the normal course of development of the lymphatic system. Through some anomaly of growth, fibrosis or other accident, the primitive jugular sac or portions of it may fail to establish a communication with the venous system. The lymphatic vessels thus sequestrated may then retain the power of inherent growth as demonstrated in the process of endothelial sprouting and penetration characteristic of the development of the normal lymphatic system.

These then, are the factors necessary for an explanation of the origin and growth of cystic hygroma.[11,12]

Accordingly then, if one accepts the above theory, cystic lymphangiomas or cystic hygromas involving the parotid area result from sequestrated lymphatic tissue which had originally penetrated this region of the head from the primitive jugular sac. Due to some accident, portions of it failed to establish a communication with the venous system. Later on, unknown

Fig. 3. Eight-month-old boy with a cystic lymphangioma of the right parotid gland area.

factors may cause activity of the inherent power of growth and penetration of this tissue, thus resulting in the cystic endothelial lined tumor involving this area. These exciting causes are not definitely known, but it has been noted in this small group of cases that in two of these children, the growth of the tumor occurred quite suddenly and progressed very rapidly following an upper respiratory infection (see Fig. 5). In the other three children, the growth was rather slow and progressive and did not appear to be related to any definite factor (see Figs. 3 and 4).

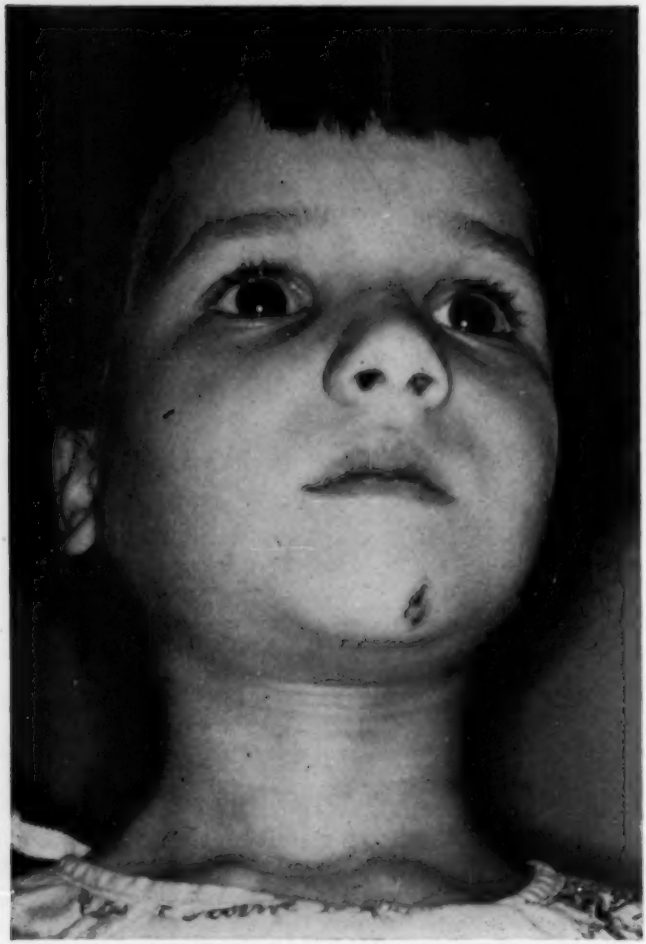

Fig. 4. Seven-year-old girl with a cystic lymphangioma of the right parotid gland area.

HISTOPATHOLOGY.

Generally speaking, there are three varieties of lymphangioma. First, simple or capillary lymphangioma which occurs quite superficially and usually involves the skin or subcutaneous tissues. The second type is cavernous lymphangioma which consists of a framework of connective tissue in which there are numerous single and communicating lymphatic cysts. There are many anastomosing channels and often irregular masses of lymphocytes, lymph nodes, and lymph follicles, and occasionally one sees neoplastic blood vessels in great numbers. When vascularity is quite great the term hemangio-lymphangioma is often applied to them. The third type, and the one with which we are concerned, is cystic lymphangioma. These are tumors with larger thin walled convoluted cysts filled with lymphatic fluid. The majority of these tumors occur in the cervical region and are often called cystic hygromas. They may be present for a considerable period of time and then suddenly begin to enlarge. Some pathologists feel that these tumors are at the onset cavernous lymphangiomas which become dilated with lymph, either as a result of a change in the drainage or an alteration in the function of the lining membrane. This sudden onset of rapid growth may be explained by a very active cell production with an inherent power of growth on the part of the endothelium. The extension of these tumors into the axilla and the mediastinum has been thought to corroborate this view.

The characteristic gross pathologic appearance of these tumors is a multilocular cystic mass in which the individual cysts vary from the size of a pinhead to that of a lemon. The walls of the younger cysts are extremely thin and often transparent; the walls of the older cysts are often thick and fibrotic. There is frequently generalized fibrosis in the older tumors and often fragments of adjacent muscles, fascia, nerves, and blood vessels are adherent to the main mass. The cysts themselves are usually soft and fluctuant but are rarely tense. The fluid within the cysts is serous, watery, clear or straw colored, and occasionally blood stained. Often the mass is intimately associated with groups of enlarged lymph nodes. The nodes are encountered in the walls of the tumor and are

doubtless directly involved in the pathologic process. The cystic spaces within the tumor are found to be lined with a thin, white, glistening, almost transparent, membrane which resembles peritoneum or pleura. The microscopic pathologic characteristics reveal these cysts to be lined with a single layer of endothelium. The older cysts are characterized by thick fibrotic walls which at times are almost avascular. Below the endothelial layer, there is often a layer of loose, extremely fine reticulum composed of a row of connective tissue resembling very fine adipose tissue. Usually in the thin and younger cysts there are dense aggregations of lymphoid cells. These vary in size from groups of a few cells to large accumulations containing true follicles with germinating centers which resemble those in lymph nodes (see Fig. 2). Goetsch has reviewed the histologic characteristics of the manner in which these tumors penetrate adjoining normal tissues. His excellent observations have demonstrated that from the growing margin of the cyst, fine delicate membranes appear as bands or cords composed of endothelium. These radiate from the wall of the cyst and in a serpentine fashion penetrate the clefts of the adjacent tissue. They terminate in several small fibrillae which are lost in the adjacent tissues. These radical sprouts in turn send off lateral branches into the tissue clefts. Between these fibrillae frequently are seen lymphoid cells and, at varying intervals along the sprouts, droplets of a foam-like faintly blue staining secretion is noted. These droplets are identical in appearance with the coagulated contents often seen in the larger and older definitely formed cystic spaces. As a result of the continued secretion, the droplets enlarge and are then enabled to spread apart and finally canalize the fibrillae. These, thereupon, form the limiting endothelial walls of the newly formed lymph capillaries and minute cysts. New cysts are brought into being by this characteristic process of secretion within and subsequent canalization of the fibrillae. The penetrating endothelial fibrillae may surround and isolate individual muscle fibers and glandular tissue which later show atrophy and degeneration.[6]

Unless infection or hemorrhage has occurred, the fluid

characteristic of cystic lymphangiomas is thin, watery, and clear or straw colored. It is particularly free of albumin and globulin and does not coagulate on cooling. A study of the sediment following centrifugation shows large numbers of lymphocytes, mononuclear cells, and cholesterol crystals.

SYMPTOMS.

Cystic lymphangioma is a disease of infancy and early childhood. These tumors are usually noted at birth and, in most instances, grow slowly; however, sometimes there is rapid growth with encroachment on vital structures of the surrounding area. In the parotid area, the tumor may appear as a soft poorly defined swelling. It is painless and is usually observed for a variable length of time before medical consultation is requested. Some investigators interested in hygroma, have pointed out the periodic fluctuation in size which has frequently been observed. This is more characteristic of the cervical type and was not noted in the five cases of involvement of the parotid area presented here. In one of these cases, the parents and family physician noted the presence of the above described soft poorly defined mass at birth (see Fig. 3). In two cases the onset of the tumor was noted within the first few years of life (see Fig. 4). This was observed by the parents and because of the cosmetic deformity they sought medical attention. In the other two cases, the growth of the tumor was quite rapid and appeared after an upper respiratory infection (see Fig. 5). Apparently the infection had led to a plugging or partial obstruction of the normal lymphatic channels so that there was a backing up of the lymph in the cystic tumor which caused it to enlarge. This would, of course, indicate communications existing between the lymphangioma and the normal lymphatic spaces.

The picture may be complicated as a result of an infection produced by an attempt at incision and drainage. Two of these cases were previously diagnosed as parotid abscesses. One had been incised and drained nine times prior to admission to the Indiana University Medical Center (see Fig. 5). The other case was aspirated and the centrifuged specimen examined microscopically. Because of the large number of

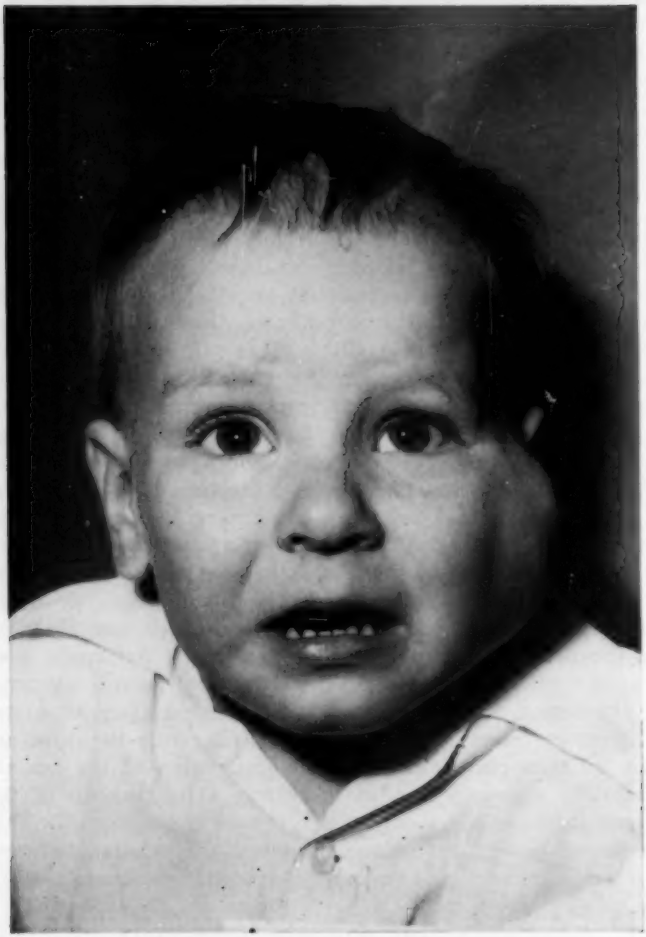

Fig. 5. Three-year-old boy with a cystic lymphangioma of the left parotid gland area. Incision and drainage had been performed nine times prior to removal of the tumor. Two other cases were similar in appearance to this child.

lymphocytes present, the possibility of cystic hygroma was strongly considered.

DIAGNOSIS.

Since the occurrence of cystic hygroma of the parotid area is unusual, diagnosis of this tumor is often not made prior to surgery. It is our feeling that the most helpful aid in diagnosis, aside from keeping in mind the possibility of such a tumor, is aspiration under sterile conditions and cytologic examination of the sediment after centrifuging the collected fluid. Cystic hygromas will usually show large numbers of lymphocytes and the absence of epithelial tissue. The two most common conditions which would simulate cystic hygroma in the parotid area, are branchial cleft cysts of the first arch, and lipomas. Branchial cleft cysts are usually associated with a dimple or a draining fistula into the external auditory canal. They are usually tense, firm, well circumscribed, and often deep seated. Aspiration of such a tumor will reveal a large amount of cholesterol present in the fluid together with presence of epithelial debris typical of the lining from such a cyst. Lipomas are more difficult to differentiate. They are usually extremely soft and poorly defined, non-tender, and are sometimes in a deep seated location. They are not as fluctuant as cystic hygromas and grow quite slowly. Other conditions which one must consider in a differential diagnosis are tubercular adenitis, abscesses of the parotid area, hemangioma, and occasionally a tumor of the malignant lymphoma group.

TREATMENT.

In the treatment of cystic lymphangioma, several forms of therapy are available. It is best to consider these individually as they may apply to location in the parotid gland region.

1. Expectant Treatment: Some investigators have advised that surgical treatment should be withheld for an indefinite period of time because of the possibility that the hygroma may undergo spontaneous regression. Most investigators are not in agreement with this idea. Although it is true that

some cysts will decrease in size, they usually refill and there is always a progression in size if a patient is followed over a long period of time.

2. Aspiration Treatment: Some authors have advised that in very young children, aspiration treatment should be used until the child is old enough to withstand surgical removal of the tumor. Repeated aspirations always are accompanied by the danger of secondary infection. If this should occur in a lesion located in the parotid area, subsequent removal would be made more difficult.

3. Injection of Sclerosing Agents Following Aspiration of the Cysts: This type of treatment has been suggested and, in tumors located in other parts of the body, is probably acceptable. Repeated aspiration of the involved area is done followed with injection of a 5 per cent solution of sodium morrhuate. This is repeated several times and after a period of a month, the mass is removed. Investigators who have studied the pathologic material available from these tumors, are in agreement that the thinness of the lining of cystic lymphangioma makes it almost ideal for injection therapy. The sclerosing agent can easily diffuse to the fluid medium and would not have to penetrate deeply into the tissues in order to destroy the endothelial layer. In the case of treatment of these tumors in the parotid area, one would have to consider possible damage to the facial nerve which may occur if the sclerosing agent were injected into branches of the nerve itself.

4. Radium or Roentgen Ray Therapy: Gorden New and Frederick Figi from the Mayo Clinic have been the principal proponents of radium therapy.[5] The cases that these investigators reported were done approximately 30 years ago. At that time, surgical excision of these tumors was considered a rather hazardous procedure in young children. In regard to treatment of cystic lymphangioma in the parotid area, it may be stated that presently radium or X-ray therapy is not an accepted therapeutic measure. The retardation effects on the future growth in this area and also the possibility of carcinogenic tendencies developing years later in individuals who

have had this type of treatment for benign lesions are contraindications for this therapy.

5. Surgical Excision: The meticulous surgical removal of cystic lymphangioma from the parotid area is the most satisfactory method of treatment. In general, the surgical procedure is similar to that used for removal of parotid tumors. The skin incisions should be in a direction which will later correspond to the normal folds in this area. The incision as used by Dr. James Maxwell of Ann Arbor, Mich., is considered the best for our purposes here. A skin flap over the parotid area is developed and carried anteriorly as far as is necessary. Dissection is carried between the external auditory canal and the parotid gland itself to the tympanic plate of the temporal bone. The tail of the parotid is separated from the anterior border of the sterno-cleido mastoid muscle, and dissection is carried deeper into the groove between the tympanic plate and the mastoid process. The main trunk of the facial nerve is then identified as it emerges from the styloid mastoid foramen. In our experience with the five cases reported here, the cystic lymphangioma seemed to originate from beneath the facial nerve in close proximity to the posterior facial vein. In one case, the cyst was so closely attached to the vein that resection of the posterior facial vein, together with the cystic hygroma, was necessary. From beneath the nerve, the tumor spreads throughout the parotid area penetrating between portions of salivary tissue, connective tissue, and fat. The tumor seems to penetrate adjacent structures following the lines of least resistance. It is interesting to note that the tumor seems to grow in an outward direction rather than to penetrate deeper structures in this area. These cysts in the parotid area are multilocular. They consist of a variation of cysts which are only a few millimeters in diameter to those which are several centimeters in size. No attempt is made to dissect each individual cyst, but the dissection is carried superficially to the facial nerve until the branches of the facial nerve have been identified in their entirety. The superficial lobe of the parotid gland together with portions of the cystic lymphangioma which involve it are first removed. Following superficial parotidectomy and removal of the hygroma

in this area, piecemeal removal is carried out beneath the nerve until the dissection has been complete. It is our feeling that it is mandatory to maintain the integrity of the facial nerve, and in doing this, it is necessary frequently to leave minute bits of lymphangiomatous tissue along their surfaces. This does not militate against a successful outcome, since apparently the small remaining islands of lymphangiomatous tissue become sclerosed and do not give rise to subsequent recurrences. A Penrose drain is brought out through a stab wound in the upper cervical region. The wound is thoroughly irrigated and the skin edges are approximated using fine silk. A pressure dressing is then applied in the usual manner. There were no cases of temporary or permanent facial paralysis following surgical management of this type, and at the present time, there have been no cases which have shown evidence of recurrence.

FIVE CASE HISTORIES.

Case 1. R.F. The patient is an eight-month-old boy who was admitted to Riley Children's Hospital in Indianapolis, Ind., because of a cystic tumor involving the right parotid gland area. The parents had noted the tumor shortly after birth. The tumor slowly increased in size although it remained painless. Physical examination and laboratory work were entirely normal. Surgery was done on December 11, 1956, and consisted of parotidectomy on the right side with removal of a cystic lymphangioma with preservation of the facial nerve. The child was discharged from the hospital on December 16, 1956. There has been no evidence of recurrence at this time.

Case 2. F.V.N. The patient is a five-year-old girl who was admitted to St. Vincent's Hospital in Indianapolis, Ind., because of a cystic tumor involving the right parotid gland region. Several weeks previously, the child had had what was thought to be unilateral mumps. Aspiration of the involved area revealed a bloody fluid which on cytological examination revealed a large number of lymphocytes. Cystic lymphangioma was entertained as the most likely diagnosis. Parotidectomy was performed on July 9, 1957, with apparent complete removal of the cystic lymphangioma.

Case 3. J.J. The patient is a three-year-old boy who was admitted to Riley Children's Hospital in Indianapolis, Ind., because of a tumor involving the left parotid gland region. Onset of this tumor was noted in May, 1958, at which time diagnosis of unilateral mumps was made. The swelling persisted and during the next five months, incision and drainage of the involved area was done nine times. Surgery was done on October 3, 1958, and consisted of parotidectomy with removal of a cystic lymphangioma involving the left parotid gland. The facial nerve was preserved intact. Follow-up to this time has revealed no evidence of recurrence.

Case 4. D.R. The patient is a two-and-a-half-year-old girl who was admitted to the Indianapolis General Hospital on October 30, 1958, be-

cause of a large pre-auricular cystic tumor involving the right parotid gland area. The tumor had been present in this region for approximately 18 months. Diagnosis of cystic lymphangioma was entertained, and surgery was done on October 31, 1958. Surgery consisted of parotidectomy with removal of cystic lymphangioma from the right parotid gland region. The facial nerve was preserved intact. The patient's postoperative course was satisfactory, and she was discharged from the hospital approximately ten days later. There has been no recurrence at this time.

Case 5. D.H. The patient is a seven-year-old girl who was admitted to the Methodist Hospital in Indianapolis, Ind., because of a cystic tumor involving the right parotid gland region. The parents had noted the onset of this tumor approximately 18 months previously, and it had slowly increased in size. Diagnosis of cystic lymphangioma of the right parotid gland area was made, and surgery was carried out on February 9, 1959. Surgery consisted of parotidectomy on the right side with removal of a cystic lymphangioma. The facial nerve was preserved intact. The postoperative course was satisfactory, and the child was discharged from the hospital on February 13, 1959. Subsequent follow-ups have revealed no evidence of recurrence to this time.

SUMMARY.

A review of the developmental anatomy of the lymphatic system and the etiology and behavior of cystic lymphangioma is presented.

Experiences with five cases of cystic lymphangioma involving the parotid area are reported.

It is the opinion of the author that the treatment of this tumor in this location is best accomplished by meticulous surgical excision.

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DEEP MYCOTIC INVOLVEMENT OF THE RIGHT MAXILLARY AND ETHMOID SINUSES, THE ORBIT AND ADJACENT STRUCTURES.

Case Report Evaluating the Use of Mycostatin Locally and Amphotericin B (Fungizone) Intravenously Against Aspergillus Flavus.*†

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The etiological agent in this case was identified to be Aspergillus flavus. The structures affected were the right maxillary sinus, the ethmoidal labyrinth, the right orbit and adjacent structures. Several references recommended the treatment of this infection[1,2,3,4,5] to be the administration of a saturated solution of potassium iodide, the surgical excision of the granuloma as far as possible, and the avoidance of irradiation therapy.[6] The use of Mycostatin (Nystatin) was suggested by the manufacturers[7,8] in February, 1956. Nystatin was the first antifungous antibiotic agent of high efficiency and low toxicity. It was derived from cultures of Streptomyces noursei. This antibiotic was used in the powdered form and insufflated into the nose and right maxillary sinus for weeks. Obviously this was only a superficial topical application.

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Later, one course of this medication was given orally. This drug was reported to be very poorly absorbed by mucous membranes or the intestinal tract. It had been used in the treatment of yeast and mycotic infections following the administration of "broad spectrum" antibiotics. There was no evidence of how repeated applications might influence this infection if it were used locally. This strain of Aspergillus flavus was sensitive to 10 micrograms per milliliter of Nystatin *in vitro*. No other more specific preparation was available at that time for the treatment of fungus infections.

In April, 1957, the first course of amphotericin B (Fungizone®)* was begun. This was given intravenously in 5 per cent glucose solution. Amphotericin B is an antibiotic formed by a species of Streptomyces isolated from a soil sample obtained in South America. A second course of treatment was started in November, 1957, a third course in February, 1959. The surgical treatment and clinical course is detailed below.

CASE STUDY.

Patient is a 31-year-old colored male, with ten years' military service, who first noted prominence of the right eye in February, 1955. This enlisted man had been a heavy equipment supervisor for the Army Corps of Engineers. He had served in Korea from 1950 to 1952, and another year in Northern Japan. In 1953 he spent six months at Camp Polk, La. He was stationed at Fort Hood, Tex., for about two years, and then sent to Fort Ord, Calif., in March, 1955. In May, 1955, while at Camp McCoy, Wisc., he came under medical observation for the exophthalmos and arrived at Fitzsimons Army Hospital in July. In March, 1955, he began to have blurred vision in the right eye. On admission to this hospital his vision was 20/50 in the right eye and 20/20 in the left eye. Vision had been 20/20 in the right eye previously. His exophthalmos measured 23 mm. in the right eye and 19 mm. in the left eye with the exophthalmometer. Fundus examination of the right eye showed horizontal striae which involved the macular area. Visual fields showed a loss of the upper portion of the field of vision above the horizontal. X-rays of the sinuses showed an increased density of the upper half of the maxillary sinus and some haziness of the inferior ethmoid cells on the right side (see Fig. 1). The right maxillary sinus was opened through the canine fossa on July 20, 1955, and a biopsy of the tissue in the upper portion of the sinus taken. The diagnosis of a non-specific granuloma was made, and the patient was given a course of antibiotic therapy, including terramycin, INH, streptomycin, and penicillin. The INH was given 300 mgs. per day until September, 29, 1955, without evident improvement of the exophthalmos.

In December, 1955, patient began to experience discomfort in the right eye. The exophthalmos remained about the same (see Fig. 2). On

*Fungizone® is a Squibb trademark. The Squibb Institute for Medical Research kindly furnished the drug for this clinical investigation.

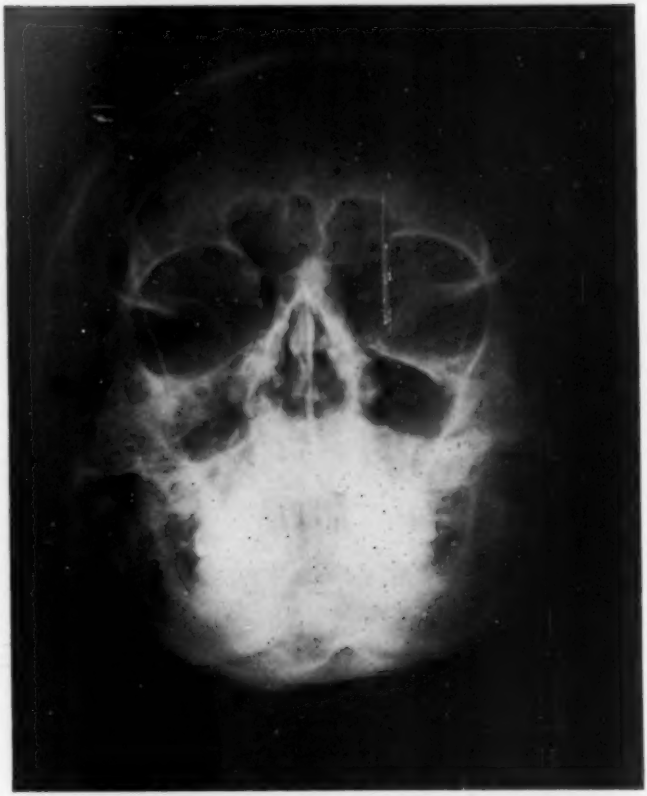

Fig. 1. X-rays (Water's view) of sinuses showing increased density upper half of the right maxillary sinus. The lower right ethmoid area is denser than the corresponding left side. There is some mottling of the body of the right malar bone.

December 13, 1955, an exploration of the right maxillary sinus and ethmoid sinuses was done using the Caldwell-Luc approach. Cultures of the tissues from the sinuses grew Aspergillus flavus. The fungus was also found in the tissues by PAS stain. As much of the granuloma as possible was removed surgically from the maxillary and ethmoidal sinuses. The bony floor of the right orbit had been eroded. There was no demarkation between the granulomatous tissue and the normal structures of the floor of the right orbit (see Figs. 3 and 4).

Postoperatively, the patient was given a saturated solution of potassium iodide, taking increasing doses up to 25 drops three times daily. Locally, Mycostatin powder was insufflated into the nose and right maxillary

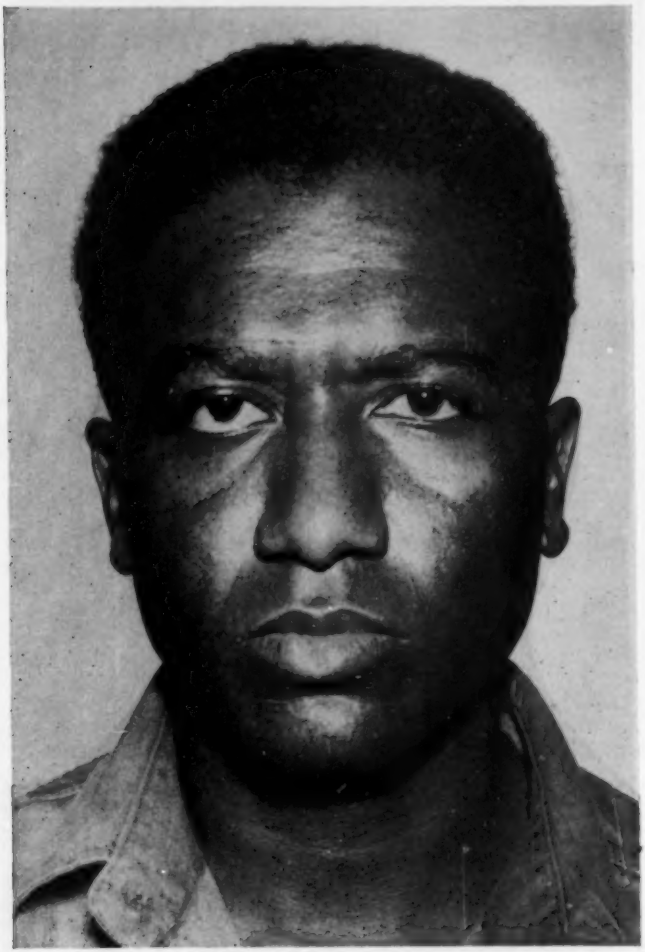

Fig. 2. Photo of patient, December, 1955. Exophthalmos right eye measures approximately 5 mm.

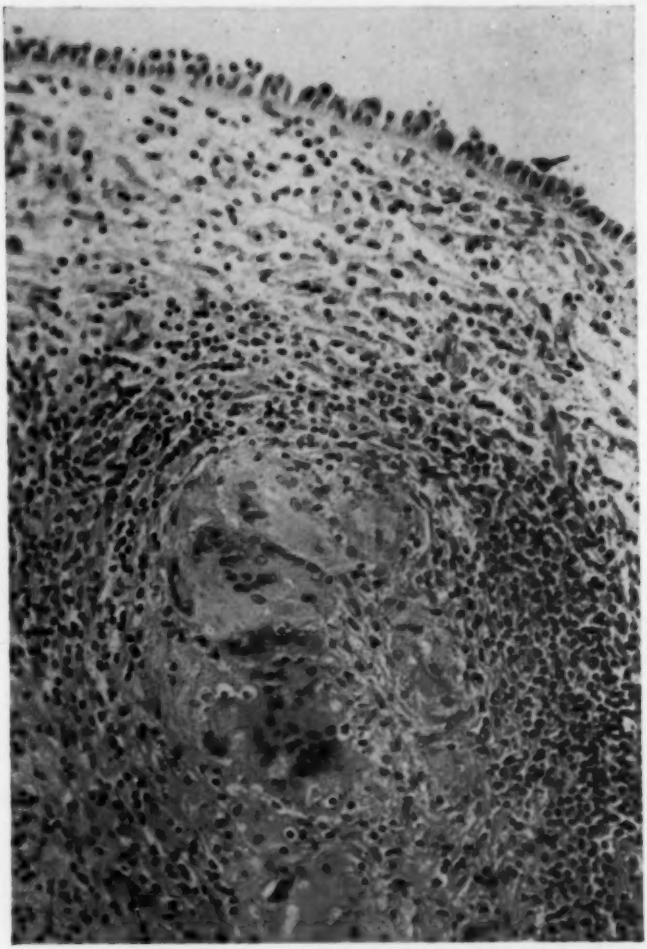

Fig. 3. Photomicrograph of tissue removed from the right maxillary sinus December 13, 1955. The respiratory epithelium is at the upper edge. The granulomatous tissue is composed of relatively young fibroblasts, with trabeculae of more mature fibrous tissue. The infiltrate is of all types of chronic inflammatory cells with numerous, scattered, multinucleated giant cells (X200).

Fig. 4. Photomicrograph of PAS stained tissue removed from right maxillary sinus December 13, 1955, showing numerous septating mycelial elements. Tissue cultures identified the Aspergillus flavus (X200).

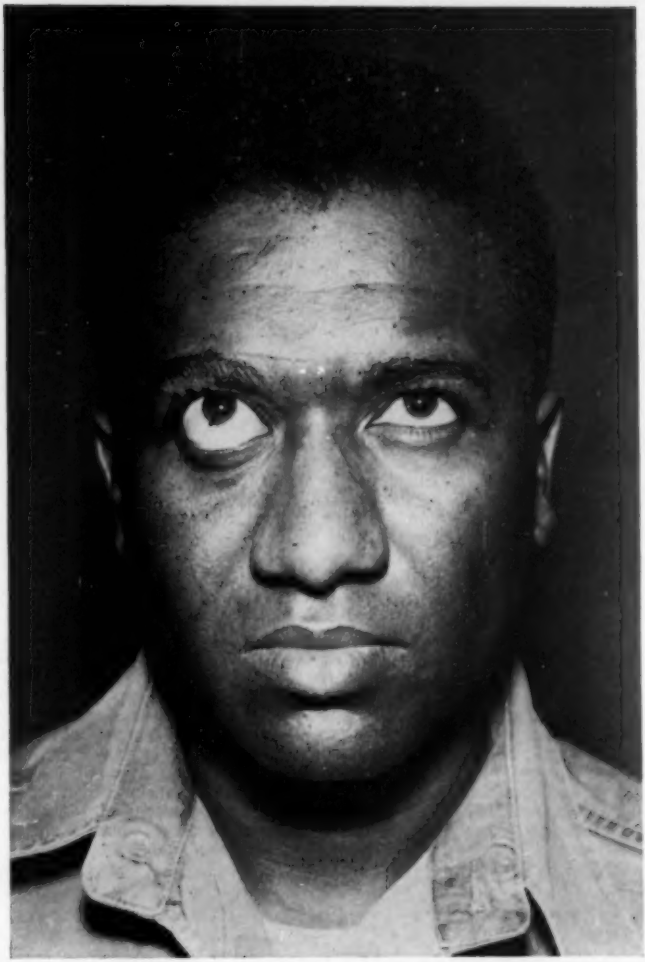

Fig. 5. Photo of patient January, 1957, at which time his exophthalmos measured 8 mm.

sinus space daily. By April, 1956, the clinical and X-ray findings of the skull seemed stabilized. Cultures of tissue removed from the nose and right maxillary sinus failed to grow fungus. Vision in the right eye was correctible to 20/20; the visual fields, fundus findings and exophthalmos remained unchanged. He was followed as an outpatient until January 14, 1957, at which time he was rehospitalized due to an increase in the exophthalmos in the right eye to 26 mm. (see Fig. 5). In March, 1957, the exophthalmos measured 28 mm. On March 19, 1957, patient was placed on four tablets of Nystatin every six hours for 12 days and then five days' treatment with eight tablets every six hours. The patient tolerated this medication without any untoward effects; in fact, he states he gained six pounds during this period. There was no noticeable change in the exophthalmos or his symptoms following this medication. His general condition was excellent.

Inasmuch as the infection appeared to be progressing in spite of the medications which had been used, it was decided to give him amphotericin B to see whether it would perhaps have some effect on this infection. In April, 1957, the use of amphotericin B (Fungizone) intravenously was begun in dosages recommended by the manufacturer.[9] Prior to use of this drug, stool cultures were negative for enteric pathogens. Complete blood counts were normal. Urinalyses were normal. Spinal fluid was examined on April 18, 1957, and the spinal fluid findings, including cell count, sugar chlorides, globulin, total protein, colloidal gold and serological tests, were normal. Culture of the spinal fluid showed no growth in 21 days. Liver and biliary function tests were normal. X-rays of the chest were reported to be normal. Stereoscopic views of the skull showed an increase in density throughout the right maxillary sinus and some mottling in the right zygoma. There also appeared to be some increased density in the petrous pyramid and some demineralization of the middle cranial fossa on the right. During this period the patient had few complaints except the decreased vision in the right eye, the proptosis, and vague aching pains which he frequently experienced in the eye.

Treatment with amphotericin B was initiated on April 23, 1957. The initial dose was 0.25 mg. per kilogram of body weight. This was increased 0.5 mg. per kilogram daily. Since the patient weighed 146 pounds, or 66 kilograms, the initial dose was 16.5 mg. The medication was given intravenously in 200 cc. of 5 per cent glucose solution slowly over a period of six hours. On May 8, 1957, the dosage had been increased to 1.00 mg. per kilogram daily. This medication was continued at this level until May 13, 1957, at which time he had received a total of 991 mg. of the medication. During the middle of this series of medications the patient remarked that he thought he was having a little less discomfort in the right eye, and he also felt that there was less swelling in the area. Examination, however, did not verify this.

The patient tolerated this medication well; however, he states that he had a chill every day that he received the drug. His temperature during the periods of medication was usually 101° to 102°, although some days it was less, and on four or five days rose to 103.2°. Near the termination of the medication the patient realized that if he took aspirin or aspirin-phenacetin-codeine compound early in the period of administration that he had less chills and felt considerably better. Most of the chills came near the last half-hour of the administration and frequently one-half hour or an hour after the medication had been finished. He complained of nausea on several occasions, anorexia on many occasions, and twice he vomited.

Inasmuch as he had shown little clinical improvement, it was decided

to give him the medication which we had on hand. Accordingly, on May 29, 1957, treatment was begun again. This time the initial medication was 1 mg. per kilogram, which was given in 300 cc. of 5 per cent glucose, and the daily dosage was increased by 0.1 mg. He received treatment six more days, receiving from 66 mg. to 92.4 mg. daily during this period. The reactions from this medication were exactly the same as he had experienced with the previous period of medication, having temperature from 98° to 102° during these six days, and having a chill every day with some nausea and anorexia. The patient received a total of 27 days' medication, with a total amount of 1,540 mg. of the drug. Post medication laboratory examinations showed normal blood counts, blood chemistry within accepted average values, and negative urinalyses. X-rays show further destruction of the walls of the right maxillary sinus and perhaps further right orbital involvement. The patient received no other medication during the treatment with amphotericin B except aspirin or aspirin-phenacetin-codeine compound. There appeared to be no improvement symptomatically or objectively.

On June 27, 1957, the right orbit was explored under local anesthesia. A fibrous mass was found in the inferior portion of the orbit, and the mass of tissue was removed piecemeal. It extended posteriorly to the region of the optic foramen and was adherent to the periosteum of the floor of the orbit. It also extended medially into the left ethmoid region. It appeared that the granuloma had developed from the roof of the right maxillary sinus and eroded through the bony floor of the orbit. Powdered Nystatin was placed in the operative site. Specimens were forwarded to the laboratory for pathological examination. The diagnosis was again confirmed on July 1, 1957, by the pathology service and again demonstrated Aspergillosis. The postoperative period was complicated by the formation of an abscess which drained through the incision on July 6, 1957. This infection gradually cleared with no more difficulty. On July 27, 1957, there was 4½ mm. of exophthalmos. The first of August the patient was feeling considerably better. The operative area was well healed, and he was given 15 days' convalescent leave, during which time he took potassium iodide drops. He was re-evaluated on August 9, 1957, and was given another convalescent leave. On September 9, 1957, the right exophthalmos measured 6½ mm. Funduscopic examination at that time continued to show some dilatation of the veins of the fundus. In October, 1957, patient was given several injections of amphotericin B diluted with procaine or xylocaine into the floor of the right orbit.[10] This procedure was quite painful to the patient, and no definite beneficial result could be noted. On November 23, 1957, he showed an exophthalmos of 8 mm., the visual acuity was 20/200 on the right correctible to 20/20, and visual acuity was 20/20 on the left. On November 26, 1957, another course of intravenous amphotericin B was started. This continued through January 2. Approximately 1,000 mg. was given during this course of therapy. The patient had his usual symptoms of some fever and chills during this period. Inasmuch as exophthalmos was progressing and the patient was again experiencing pain, it was decided that further surgical intervention was necessary. On December 2, 1957, under endotracheal anesthesia, the patient had a removal of granulations and adjacent bone of the right maxillary sinus, the floor of the right orbit, and the structures of the lateral wall of the right nasal passage. The granuloma involving the floor of the orbit was removed as completely as possible; however, fibrosis seemed to extend posteriorly beneath the optic nerve. Two units of blood were given following this procedure and the course of intravenous amphotericin, which had been started on November 26, 1957, was continued. The procedure decompressed the orbit from below and medially, lessened the exophthalmos, and provided the

patient with a considerable degree of comfort. X-rays following this procedure showed essentially the same findings with the exception of the operative defect. The operative site healed quickly with no complications. For the next six to eight weeks the patient was seen daily, the nose was cleansed, and Nystatin powder again dusted into the operative cavity through the right side of the nose. Tissue cultures again grew fungus. On December 20, 1957, the blood levels of amphotericin B after the daily dosage of 1 mg. per kilo body weight were determined to be 0.2-0.4 mcg./ml.

Early in February, 1958, the patient began to notice a swollen area just above and anterior to the right ear. This area has continued to be present; however, it varies in size from time to time. The area is not tender and appears to be more of a transitory edema than an extension of the infective process. Vision is 20/100 in the right eye, and 20/20 in the left eye; correctible in the right eye to 20/20; however, the patient is unable to wear lenses because of the exophthalmos. The retina, right eye, shows stria around the posterior pole from retrobulbar pressure. Exophthalmos is 6 mm. in the right eye.

The patient has been temporarily retired from active military service. He has been followed on an outpatient status. Tissue biopsies from the lateral wall of the right nasal passage on June 25, August 16, and November 4, 1958, were cultured and have failed to grow Aspergillus. On November 13, 1958, some tissue was removed from the midportion of the floor of the right orbit, going through the right inferior fornix. Three separate specimens were taken. These three fungus cultures were negative after 26 days. The patient's general condition was excellent on examination November 20, 1958. He had a right exophthalmos of 6-7 mm. Vision in the right eye was 20/70 correctible to 20/25, and 20/20 in the left eye. The fundus of the right eye showed horizontal striae or traction lines extending through the macular area. X-rays of the sinuses and skull showed little, if any, change during the last nine months.

Due to the slowly increasing proptosis of the right eye, more evident swelling of the right temple area and more pain in the right cheek, the patient was rehospitalized on February 20, 1959. Despite the recent negative tissue cultures, it was evident there was recurrent activity of the granuloma. Another course of amphotericin B intravenously was begun the next day, using the same dosage schedule as given above. On February 24, 1959, under endotracheal anesthesia the right temporal fossa was explored through a horizontal incision extending posteriorly from the external canthus of the right eye. Granulomatous tissue had eroded the lateral bony orbital wall near the floor about 3 cm. posterior to the lateral orbital rim. The involved temporal muscle was removed. The bone of the lateral wall of the orbit was removed. A large granulomatous mass was encountered beneath and lateral to the globe. This was excised by blunt and sharp dissection. There were areas of necrosis in the temporal fossa and in the floor of the orbit. There were also areas of firm fibrotic material. The granuloma extended to the apex of the orbit and beneath this into the pterygomaxillary space. There was direct extension of the fibrous tissue into the right maxillary sinus space. Dependent drainage was established through the floor of the orbit into the sinus and into the nose through the previously placed window in the medial sinus wall. A mushroom tipped catheter was placed in the right maxillary sinus. The superior aspects of the orbit seemed to be free of involvement. A large Penrose drain was sutured in the initial incision. The intravenous administration of amphotericin B was continued postoperatively for a total of 900 mg. Locally, the postoperative course was accompanied by protracted conjunctival edema. Gradually the tissues

resumed a fairly normal appearance. The position of the right globe was very nearly normal. Measurements for exophthalmos were less reliable since the right lateral bony rim had been removed.

The microscopic tissue studies show granulomatous inflammation with areas of necrosis. There are predominantly lymphocytes with numerous giant cells, some of these showing hyphae. Tissue culture yielded an abundant growth of the Aspergillus species. Patient was discharged April 14, 1959, after 54 days of hospitalization.

The minimal inhibitory concentration by the multiple tube dilution test for this patient's fungus is given below and is contrasted with the blood levels obtained after the administration of amphotericin B.

Sensitivity M.I.C. (Minimum Inhibitory Concentration).

Tissue Culture of	Amphotericin B	Nystatin
December, 1955	6 mcg./ml.	10 mcg./ml. 40 units
June, 1957	3 mcg./ml.	40 units
February, 1959	2-5 mcg./ml.	5-50 units/ml.

Blood concentration (serum activity) of amphotericin B, after dosage of 1 mg. per kilo administered intravenously, was 0.2-0.4 mcg./ml. maintained over a 12-hour period. Obviously, this is much below the minimum inhibitory concentration level for this patient's aspergillus infection.

This patient has operated his own truck during the summer and fall of 1959. He reported for examination September 19, 1959. His vision was O.D. 20/100, O.S. 20/20; correctible to 20/25 on the right. The proptosis was measured as 6 mm. variation between the two corneas. There was limitation of adduction on the right. The right fundus shows wrinkling of the retina. Patient could not wear correcting lenses due to the exophthalmos. Blood pressure was 140 mg. systolic, 80 diastolic.

Patient was readmitted to hospital on December 8, 1959. There was definite increase of the proptosis of the right eye. The vision was 20/80, correctible to 20/40. There is a noticeable exotropia. The fundus picture is the same as described above with the wrinkling or stria about the macular area being visible. The patient complains of constant pain over the right cheek. There is no particular palpable change in the tissues locally (see Fig. 6). It is possible that this complaint is based upon the pressure or infiltration of the second division of the Vth cranial nerve. This could mean further extension of the granuloma in the middle cranial fossa. Examination of the nasopharynx is negative. The general condition is excellent except that this patient presents with a blood pressure of 240 systolic, 120 diastolic. He is at present under medical treatment, which has precluded surgical treatment requiring the administration of a general anesthetic. Liver function tests and blood studies are within normal limits. There is evidence of some nitrogen retention as indicated by a slightly elevated blood urea nitrogen.

TOXICITY.

Within the dosage schedule used in the treatment of this patient with amphotericin B intravenously, the toxic effects

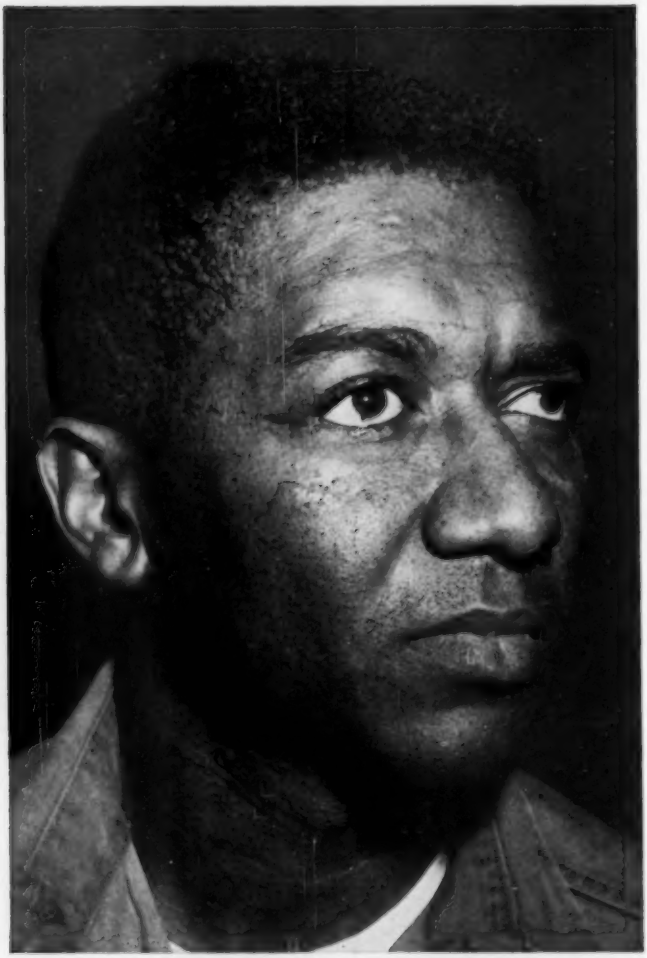

Fig. 6. Appearance of patient in December, 1959, after surgical decompression of the right orbit below, medially and laterally, Nystatin locally and three courses of Fungizone. There is recurrent fullness of the right temporal area and an increase in the exophthalmos of approximately 6 mm. in the past several months. This is believed to indicate further growth of the granuloma within the orbit.

TABLE I.

Outline of Therapy.

Date	Clinical Symptoms	Antibiotic Therapy	Surgical Procedures	Nystatin Therapy	Amphotericin B (Fungizone)
Feb., 1955 —	Onset diminishing vision and exophthalmos, right eye.				
July 8, 1955—	O.D. 23 mm. O.S. 19 mm. O.D. 20/50 O.S. 20/20				
July 20, 1955—		Terramycin, INH Streptomycin Penicillin	Biopsy, right maxillary sinus.		
		INH 300 mg. Strept. gm. I q3d to Sept. 29.			
Aug.-Dec., 1955—	Increasing scotomata above macula.				
Dec. 13, 1955—	O.D. 21 mm. O.S. 16 mm. Vision same. Increasing pain, right eye.	Penicillin and Streptomycin 4 days.	Caldwell-Luc operation. Tissue removed right maxillary and ethmoid sinuses.		

TABLE I (Cont.).

Outline of Therapy.

Date	Clinical Symptoms	Antibiotic Therapy	Surgical Procedures	Nystatin Therapy	Amphotericin B (Fungizone)
Dec. 22, 1955—				Powder insufflated into right maxillary sinus daily.	
Jan. 11, 1956—	Tissue culture, lining right maxillary sinus—no growth.				
Feb. 15, 1956—	O.D. 22 mm. O.S. 17 mm. Base 102. Altitudinal hemianopsia, same past 2 months. Macula spared. Macular striations.			Powder continued.	
April 5, 1956—	Returned to duty. Followed as Outpatient. Sat. Sol. KI continued.				
Apr. 12, 1956—	Tissue culture, lining right maxillary sinus—no growth.				
May to Dec., 1956—	Increase in symptoms.				
Jan. 14, 1957—	Admitted to hospital. More pain. O.D. 26 mm. O.S. 18 mm. Base 103.				
Mar. 19, 1957—	Gained 6 lbs.			Oral: 4 tablets q6h for 12 days; 8 tablets q6h for 5 days.	
Apr. 23, 1957—					1,540 mg. i.v. in 27 days.

June 27, 1957—	Achromycin 6 days.	Floor right orbit explored. Firm tissue removed. Local.		
July 3, 1957—		Abscess drained through right cheek.		
Oct. 14, 1957—				4 local injections of ½ mg. drug. Painful even with 2 per cent procaine.
Nov. 26, 1957—	O.D. 26+ mm. O.S. 18 mm. O.D. 20/200. O.S. 20/20.			1,000 mg. i.v. in 23 days.
Dec. 2, 1957—		Removal floor and medial wall, right orbit.	Nose powdered postoperatively.	
Apr. 15, 1958—	Retired from military service.			
Feb. 21, 1959—				900 mg. i.v. in 20 days.
Feb. 24, 1959—		Removal of granuloma, right temporal fossa and orbit. Removal lateral bony wall.		
Sept. 23, 1959—	Retirement re-examination.			
Dec. 8, 1959—	Admitted to hospital. 1. Exophthalmos 6 mm. 2. Swelling right temple. 3. Pain right cheek. 4. Hypertension.			

observed were principally, *1.* a chill and febrile response, *2.* sensation of nausea and anorexia with occasional vomiting, *3.* headache and general malaise which were lessened by aspirin or aspirin-phenacetin-codeine compound.

It should be recalled that this patient's general bodily condition has been excellent. His laboratory examinations, including blood, liver function, intestinal cultures, and cerebral spinal fluid tests, have shown little if any variation from average normal findings until the present admission. The cause of the elevation of the blood urea nitrogen could possibly

TABLE II.

Outline of Therapy.

	Tissue	
Date of Surgery	Pathology	Culture
July 20, 1955	Granuloma	
Dec. 13, 1955	Granuloma	Positive for Aspergillus flavus.
Jan. 11, 1956 (Maxillary Sinus Biopsy)		Negative.
April 12, 1956 (Maxillary Sinus Biopsy		Negative.
June 27, 1957	Granuloma	Positive for Aspergillus flavus.
Dec. 2, 1957	Granuloma	Positive for Aspergillus flavus.
June 25, 1958 (Nasal Biopsy)		Negative.
Aug. 16, 1958 (Nasal Biopsy)		Negative.
Nov. 4, 1958 (Nasal Biopsy)		Negative.
Nov. 13, 1958 (Orbital Biopsy)		Negative after 26 days.
Feb. 24, 1959	Granuloma	Positive for Aspergillus flavus.

be attributed to a late complication of amphotericin B therapy. Other cases treated at this hospital with the same drug have not shown this residuum.[11] His reaction to this therapy would be expected to be much better than in a chronically ill or emaciated patient.

SUMMARY.

This is a case report of a 31-year-old colored male who noted unilateral exophthalmos in February, 1955. A granulomatous type of tissue was present in the right maxillary sinus which showed no response to antibiotic therapy. Cultures of tissue subsequently removed from the right maxillary antrum were positive for Aspergillus—later identified as Aspergillus flavus. Nystatin was used locally in the sinus

and a solution of potassium iodide taken orally. A short course of Nystatin was given by mouth. In April, 1957, amphotericin B (Fungizone®) was given intravenously. Cultures of tissue removed from the floor of the right orbit were again positive for the same fungus in June, 1957. The tissue removed was much firmer than that previously removed from the right maxillary and ethmoid sinuses. The pathological picture was similar. Local injections of amphotericin B into the right inferior orbit were quite painful. Decompression of the right orbit below and medially again yielded positive tissue fungus cultures in December, 1957. At this surgical exploration there was definite involvement of the pterygomaxillary fossae and about the right optic foramen. A second course of amphotericin B was given intravenously. Nasal tissue cultures and cultures of tissue removed from the midportion of the floor of the right orbit in November, 1958, have shown no fungus growth after 26 days. The patient's general condition has remained excellent. The exophthalmos was stabilized at 6-7 mm. Due to an increase of the proptosis of the right eye, a lateral decompression of the right orbit was performed February 24, 1959. A large mass of granulomatous material was removed from the inferior portion of the orbit. The granuloma extended posteriorly below the optic foramen. A third course of amphotericin B was administered. Tissue cultures were positive for Aspergillus flavus. Patient was re-admitted to the hospital December 8, 1959, for further evaluation.

The prognosis in this patient should be guarded. Local applications of Nystatin powder and three courses of amphotericin B may have retarded advance of the granuloma but have not halted the process. This is believed to be due to the inability to get a sufficiently high blood concentration of the drug to produce a favorable clinical response against this patient's Aspergillus flavus infection.

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Secretary:
Meeting:

FORT WORTH EYE, EAR, NOSE AND THROAT SOCIETY.

President: Dr. Van D. Rathgeber.
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Secretary-Treasurer: Dr. Paul Rockwell.

GREATER MIAMI EYE, EAR, NOSE AND THROAT SOCIETY.

President: Dr. Mariano C. Caballero.
Vice-President: Dr. Joseph Freeman.
Secretary-Treasurer: Dr. H. Carlton Howard.
Meeting: Quarterly in March, May, October and December on the second Thursday of the month, 6:30 P.M., at the McAllister Hotel, Miami, Fla.

INTERNATIONAL BRONCHOESOPHAGOLOGICAL SOCIETY.

President: Dr. Jo Ono, Tokyo, Japan.
Secretary: Dr. Chevalier L. Jackson, 3401 N. Broad St., Philadelphia 40, Pa., U. S. A.
Meeting:

KANSAS CITY SOCIETY OF OTOLARYNGOLOGY AND OPHTHALMOLOGY.

President: Dr. Clarence H. Steele.
President-Elect: Dr. Dick H. Underwood.
Secretary: Dr. James T. Robison, 4620 J. C. Nichols Parkway, Kansas City, Mo.
Meeting: Third Thursday of November, January, February and April.

LOS ANGELES SOCIETY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY.

President: Dr. Max E. Pohlman.
Secretary-Treasurer: Dr. Wendell C. Irvine.
Chairman of Ophthalmology Section: Dr. Carroll A. McCoy.
Secretary of Ophthalmology Section: Dr. Philip D. Shanedling.
Chairman of Otolaryngology Section: Dr. Robert W. Godwin.
Secretary of Otolaryngology Section: Dr. Francis O'N. Morris.
Place: Los Angeles County Medical Association Bldg., 1925 Wilshire Blvd., Los Angeles, Calif.
Time: 6:30 P.M. last Monday of each month from September to June, inclusive—Otolaryngology Section. 6:30, first Thursday of each month from September to June, inclusive—Ophthalmology Section.

LOUISIANA-MISSISSIPPI OPHTHALMOLOGICAL AND OTOLARYNGOLOGICAL SOCIETY.

President: Dr. Arthur V. Hays.
Secretary: Dr. Edley H. Jones, 1301 Washington St., Vicksburg, Miss.
Meeting: Edgewater Gulf Hotel, Edgewater Park, Miss., May 12-13, 1961.

MEMPHIS SOCIETY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY.

Chairman: Members serve as chairman in alphabetical order monthly.
Secretary-Treasurer: Dr. Roland H. Myers, 1720 Exchange Bldg., Memphis, Tenn.
Assistant Secretary-Treasurer: Dr. William F. Murrah, Jr., Exchange Bldg., Memphis, Tenn.
Meeting: Second Tuesday in each month at 8:00 P.M. at Memphis Eye, Nose and Throat Hospital.

MEXICAN ASSOCIATION OF PLASTIC SURGEONS.

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MEXICAN SOCIETY OF OTOLARYNGOLOGY.

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Secretary: Dr. Carlos Valenzuela, Petrarca 332-1, Mexico 5, D. F.

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(Nederlandsche Keel-Neus-Oorheelkundige Vereeniging.)

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Treasurer: Mrs. F. Velleman-Pinto, Jac. Ohrechtstr. 66, Amsterdam.

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Vice-President: Dr. George E. Bradord, Winston-Salem, N. C.
Secretary-Treasurer: Dr. J. D. Stratton, 1012 Kings Drive, Charlotte 7, N. C.
Meeting:

NORTH OF ENGLAND OTOLARYNGOLOGICAL SOCIETY.

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Vice-President: Mr. J. H. Otty, Frizley Old Hall, Frizinghall Road, Bradford, Yorkshire.
Secretary and Treasurer: Mr. R. Thomas, 27 High Petergate, York, Yorkshire.

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President: Dr. David D. DeWeese, 1216 S. W. Yamhill St., Portland 5, Ore.
Secretary-Treasurer: Dr. Paul B. Myers, 223 Medical Dental Bldg., Portland 5, Ore.
Meeting: Fourth Tuesday of each month from September through May, Henry Thiele Restaurant, 23rd and W. Burnside, Portland, Ore.

OTOSCLEROSIS STUDY GROUP.

President: Dr. E. H. Campbell, 133 So. 36th St., Philadelphia 4, Pa.
Secretary-Treasurer: Dr. Raymond Jordan, 121 University Place, Pittsburgh, Pa.
Meeting: Palmer House, Chicago, Ill., October, 1960.

PACIFIC COAST OTO-OPHTHALMOLOGICAL SOCIETY.

President: Dr. John F. Tolan, 1118 - 9th Ave., Seattle 5, Wash.
Secretary-Treasurer: Dr. Homer E. Smith, 686 Twelfth Ave., Salt Lake City, Utah.
Meeting:

PAN AMERICAN ASSOCIATION OF OTO-RHINO-LARYNGOLOGY AND BRONCHO-ESOPHAGOLOGY.

President: Dr. Paul Holinger, 700 No. Michigan Blvd., Chicago, Ill.
Executive Secretary: Dr. Chevalier L. Jackson, 3401 No. Broad St., Philadelphia 40, Pa., U. S. A.
Meeting: Seventh Pan American Congress of Oto-Rhino-Laryngology and Broncho-Esophagology.
Time and Place:

PHILADELPHIA LARYNGOLOGICAL SOCIETY.

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SIXTH INTERNATIONAL CONGRESS ON DISEASES OF THE CHEST.

Meeting: University of Vienna, August 29 to September 1, 1960.

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Ophthalmology: Dr. Warren A. Wilson, 1930 Wilshire Blvd., Los Angeles 57, Calif.
Mid-Winter Clinical Convention annually, the last two weeks in January at Los Angeles, Calif.

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Meetings are held the second Tuesday of September, November, January, March and May, at 6:30 P.M.
Place: Army and Navy Club, Washington, D. C.

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Dr. Antonio Cancela de Amorim.
Sede: Avenida da Liberdade, 65, 1°, Lisboa.

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President: Capt. Maurice Schiff, MC, USN, U. S. Naval Hospital, Oakland, Calif.
Secretary-Treasurer: Lt. Col. James E. Lett, USAF, MC, 209 Tamworth, San Antonio 13, Tex.
Meeting: Concurrent with the Academy of Ophthalmology and Otolaryngology, Chicago, Ill., October, 1960.

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Vice-President: Dr. David Stack, Spartanburg, S. C.
Secretary-Treasurer: Dr. Roderick Macdonald, Rock Hill, S. C.
Meeting: Jointly with the North Carolina Eye, Ear, Nose and Throat Society in Greenboro, N. C. Headquarters will be in the King Cotton Hotel, Sept. 13-15, 1960.

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(United Kingdom)

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Vice-Chairman: Dr. Bernard J. McMahon, Director of the Department and Clinical Professor of Otolaryngology, St. Louis University School of Medicine, 8230 Forsythe Blvd., Clayton 24, Mo.
Secretary: Dr. Albert C. Esposito, First Huntington National Bank Building, Huntington, W. Va. Formerly instructor of Ophthalmology, Ohio State University College of Medicine, Columbus, O.
Meeting: St. Louis, Mo., October 31, 1960, to November 3, 1960.

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